PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 519/00, A61K 31/4985, 31/437, 31/4375, A61P 25/00, C07D 487/04, 471/04, 455/02 // (C07D 519/00, 487:00, 471:00) (C07D 487/04, 241:00, 209:00)

A3

(11) International Publication Number: **WO 00/35919**

(43) International Publication Date: 22 June 2000 (22.06.00)

(21) International Application Number: PCT/EP99/09564

(22) International Filing Date: 3 December 1999 (03.12.99)

(30) Priority Data:
9827882.3 17 December 1998 (17.12.98) GB

(71) Applicant (*for all designated States except US*): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): GASTER, Laramie, Mary [GB/GB]; New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). HEIGHTMAN, Tom, Daniel [GB/GB]; New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

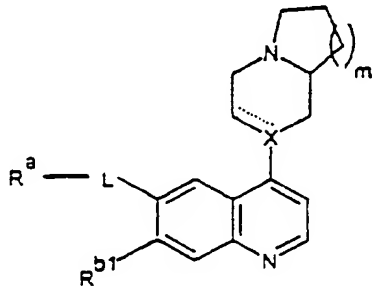
(74) Agent: WATERS, David, Martin; Corporate Intellectual Property, SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(88) Date of publication of the international search report:
26 October 2000 (26.10.00)

(54) **Title:** QUINOLINE DERIVATIVES



(57) **Abstract**

The invention relates to novel quinoline derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

Inter ɔnal Application No
PCT/EP 99/09564

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D519/00 A61K31/4985 A61K31/437 A61K31/4375 A61P25/00 C07D487/04 C07D471/04 C07D455/02 //(C07D519/00,487:00, 471:00),(C07D487/04,241:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 06644 A (SMITHKLINE BEECHAM) 9 March 1995 (1995-03-09) page 7, line 14 - line 27; claim 1	1,9
A	WO 98 50358 A (SMITHKLINE BEECHAM) 12 November 1998 (1998-11-12) page 14, line 20 -page 15, line 2; claim 1	1,9
A	WO 98 47868 A (SMITHKLINE BEECHAM PL) 29 October 1998 (1998-10-29) page 7, line 27 -page 8, line 9; claim 1	1,9
P,A	WO 99 31086 A (SMITHKLINE BEECHAM PLC (GB)) 24 June 1999 (1999-06-24) abstract	1,9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2000	24/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Alfaro Faus, I

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter: nal Application No
PCT/EP 99/09564

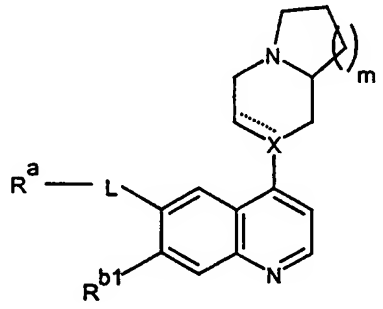
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9506644 A	09-03-1995	EP 0716656 A	19-06-1996
		JP 9502176 T	04-03-1997
WO 9850358 A	12-11-1998	AU 7431098 A	27-11-1998
		EP 0975593 A	02-02-2000
		NO 995065 A	15-10-1999
WO 9847868 A	29-10-1998	NONE	
WO 9931086 A	24-06-1999	NONE	

COMPOUNDS

The present invention relates to novel quinoline derivatives, processes for their preparation, and pharmaceutical compositions containing them.

US patent 5,703,072 discloses bicyclic nonane and decane compounds having dopamine receptor affinity which are claimed to be of use in the treatment of schizophrenia. WO 98/50358, WO 98/50346, WO 98/47868, WO 98/47885 and WO 98/50343 all disclose a series of novel compounds which are claimed to possess combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor antagonist activity and are useful in the treatment of various CNS disorders. WO 97/36867 and WO 98/14433 both disclose a series of lactam derivatives that are claimed to be selective agonist or antagonists of one or both of 5-HT_{1A} and 5-HT_{1D} receptors.

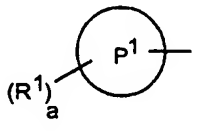
A structurally distinct class of compounds have now been found that exhibit combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor affinity. It is expected that such compounds will be useful for the treatment and prophylaxis of various disorders. In a first aspect, the present invention therefore provides a compound of formula (I) or a salt thereof:



(I)

in which R^a is selected from a group of formula (i) or (ii);

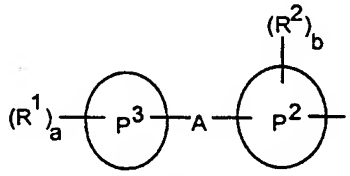
Group of formula (i)



(i)

wherein P^1 is phenyl, bicyclic aryl, C_{3-6}cycloalkyl, a 5 to 7 membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur; R^1 is halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, NO_2, CF_3, CN, SR^9, SOR^9, SO_2R^9, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $CONR^{10}R^{11}$, $CONR^{10}(CH_2)_cCO_2R^{11}$, $(CH_2)_cNR^{10}R^{11}$, $(CH_2)_cCONR^{10}R^{11}$, $(CH_2)_cNR^{10}COR^{11}$, $(CH_2)_cCO_2C_{1-6}$alkyl, $CO_2(CH_2)_cOR^{10}$, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CONR^{10}R^{11}$, $CR^{10}=NOR^{11}$, $CNR^{10}=NOR^{11}$, where R^9, R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl and c is 1 to 4; and
a is 0, 1, 2 or 3;

Group of formula (ii)



(ii)

wherein P^2 and P^3 are independently phenyl, bicyclic aryl, a 5 to 7 membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic heterocyclic group containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur; A is a bond, O, $S(O)_n$ where n is 0 to 2, carbonyl, CH_2 or NR^4 where R^4 is hydrogen or C_{1-6}alkyl;
R^1 and R^2 are independently as defined above for R^1 in formula (i); and
a and b are independently 0, 1, 2 or 3;

L is a group of formula
- Y-C(= O)-DG - or -C(= O)-DG- or -DG-C(= O)-
in which Y is NH, NR^5 where R^5 is C_{1-6}alkyl, or Y is CH_2, O, CH = CH, or OCH_2;
D is nitrogen, carbon or a CH group, G is hydrogen or C_{1-6}alkyl providing that D is nitrogen or a CH group, or G together with R^{b1} forms a group W where W is $(CR^{16}R^{17})_t$ in which t is 2, 3 or 4 and R^{16} and R^{17} are independently hydrogen or C_{1-6}alkyl or W is $(CR^{16}R^{17})_u$-J where u is 0, 1, 2 or 3 and J is oxygen, sulphur, $CR^{16}=CR^{17}$, $CR^{16}=N$, $=CR^{16}O$, $=CR^{16}S$ or $=CR^{16}$-NR^{17} provided that u is not 0 when J is oxygen or sulphur;

R^{b1} is hydrogen or together with G forms a group W as defined above;
X is nitrogen, carbon or a CH,

—— is a single bond when X is nitrogen or CH and is a double bond when X is carbon.
m is 1, 2 or 3.

C_{1-6}alkyl groups whether alone or as part of another group may be straight chain or branched. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine. The bicyclic aryl group represented by P^1, P^2 or P^3, which may be partially saturated, is preferably naphthyl. Where used herein the term naphthyl is intended, unless otherwise stated, to denote both naphth-1-yl and naphth-2-yl groups.

Within the definition of R^a formula (i)

When P^1 is C_{3-6}cycloalkyl preferred examples are cyclopentyl and cyclohexyl. When P^1 is a 5 to 7 membered heterocyclic ring suitable examples include 5 or 6 membered heteroaryl rings such as thienyl, furyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrimidyl, pyrazinyl and pyridyl. Non aromatic 5 to 7 membered heterocyclic rings include pyrrolidinyl, piperidinyl or piperazinyl. When P^1 is a bicyclic heterocyclic ring suitable examples include benzofused rings such as quinolinyl, isoquinolinyl, indolyl, benzofuryl, benzothienyl and benzo[1,3]dioxolyl. The heterocyclic and bicyclic heterocyclic groups listed above can be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom. Preferably P^1 is phenyl, naphthyl, quinolyl, pyridyl or thienyl.

When a is greater than 1 the groups R^1 can be the same or different. Preferably a is 0, 1 or 2. Preferred R^1 groups include halogen (particularly chlorine), a C_{1-6}alkyl group (particularly methyl), CN, CF_3 or a C_{1-6}alkoxy group (particularly methoxy or ethoxy).

Within the definition of R^a formula (ii)

When P^2 and/or P^3 is a 5 to 7 membered heterocyclic ring or a bicyclic heterocyclic group, suitable examples include those listed for P^1 above. Preferably P^2 is phenyl, naphthyl, pyridyl, thienyl or furyl. A preferred substitution arrangement for naphthyl groups is 1,4 or more preferably 1,5, that is to say, a naphth-1-yl group in which the group A is attached at the 4 or 5 position respectively.

Preferably P^3 is phenyl, pyridyl, thienyl, pyrazolyl or oxazolyl.

When a and/or b is 2 the groups R^1 and/or R^2 respectively can be the same or different. Preferred R^1 and/or R^2 groups include halogen (particularly chlorine), a C_{1-6}alkyl group (particularly methyl), CN, CF_3 or a C_{1-6}alkoxy group (particularly methoxy or ethoxy).

A is preferably a bond or oxygen, most preferably a bond.

Preferably L is a group of formula:-

- Y-C(= O)-DG - or -C(= O)-DG-

in which Y is preferably NH or CH_2, D is preferably nitrogen and G is preferably a hydrogen atom or together with R^{b1} forms a further group W, preferably $(CH_2)_2$, $(CH_2)_3$ or CH =CH, most preferably $(CH_2)_2$.

R^{b1} is preferably hydrogen or together with G forms a group W referred to above.

X is preferably a nitrogen atom, and m is preferably 1 or 2, most preferably 1.

Particularly preferred compounds according to this invention are:-

(S)-(-)-N-[4-(Octahydropyrrolo[1,2-a]pyrazin-2-yl)quinolin-6-yl]-3,4-dichlorobenzamide,

(S)-(-)-N-[4-(Octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinolin-6-yl]-3,4-dichlorobenzamide,

(S)-(-)-2,3-Dihydro-1-[5-(2,6-dimethylpyridin-4-yl)naphth-1-ylcarbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,

(S)-(-)-6-[5-(5-Methylpyridin-2-yl)naphth-1-oylamino]-4-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinoline,

(S)-(-)-6-(2,3-Dichlorobenzoylamino]-4-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinoline,

(S)-(-)-1-(2,3-Dichlorobenzoyl)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,

(S)-(-)-2,3-Dihydro-1-[4-(5-methyloxazol-2-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline

(S)-(-)-2,3-Dihydro-1-[5-(5-methylpyridin-2-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline trifluoroacetate

(S)-(-)-2,3-Dihydro-1-[5-(2,5-dimethylpyridin-4-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,

(S)-(-)-2,3-Dihydro-1-[5-(6-methylpyridin-2-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,

(S)-(-)-2,3-Dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)-1-(quinolin-4-ylcarbonyl)pyrrolo[2,3-*g*]quinoline,

(S)-(-)-2,3-Dihydro-1-[5-(2-methyloxazol-5-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-[5-(3-methylisoxazol-5-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-1-[5-(6-methylpyridin-2-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-1-(4-chlorobenzoyl)-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-[2-(4-chlorophenyl)-3-trifluoromethylpyrazole-4-carbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-[5-(2-methyl-5-trifluoromethylpyrazol-3-yl)-thiophen-2-carbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-(5-chlorothiophen-2-carbonyl)-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-[1-methyl-7-(2-methylpyridin-6-yl)indol-3-carbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-[5-(5-methyloxazol-2-yl)naphth-1-ylacetyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-[5-(2,6-dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline
or a pharmaceutically acceptable salts thereof.

Other preferred compounds of this invention include examples E6 – E9, E25 - E72 and E75 - E80 (as tabulated below) or a pharmaceutically acceptable salt thereof. A particularly preferred compound of this invention is E23.

Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts. These include acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates.

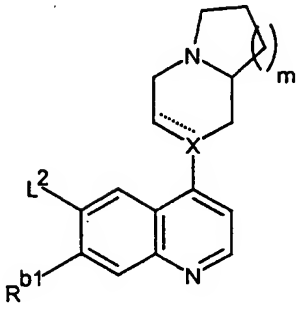
Compounds of the invention can be prepared using procedures known in the art. In a further aspect the present invention provides a process for the preparation of a compound of formula (I) which comprises:

(a) where L is -C(=O)-DG - or -DG-(C=O)-, coupling a compound of formula (II):

R^a -L^1

(II)

with a compound of formula (III):



(III)

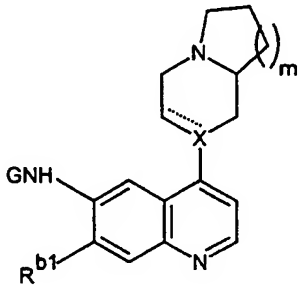
in which R^a, R^{b1}, X and m are as defined in formula (I) and L^1 and L^2 contain the appropriate functional groups which are capable of reacting together to form the L moiety; or

(b) where L is - Y -C(=O)-DG in which D is nitrogen and Y is NH, coupling a compound of formula (IV):

R^a -NC(=O)

(IV)

in which R^a is as defined in formula (I) or a protected derivative thereof, with a compound of formula (V):



(V)

in which R^{b1}, X, m and G are as defined in formula (I), or a protected derivative thereof; or

(c) where L is - Y -C(=O)-DG - in which D is nitrogen and Y is NH or NR^5, reacting a compound of formula (VI)

R^a -NH_2 or R^a -NR^5H

(VI)

in which R^a and R^5 are as defined in formula (I) with a compound of formula (V) together with an appropriate urea forming agent; or

(d) where L is - Y -C(=O)-DG - in which D is nitrogen and Y is CH_2 or O, reacting a compound of formula (VII):

$$R^a\text{-}Y\text{-}(C{=}O)\text{-}L^3$$

(VII)

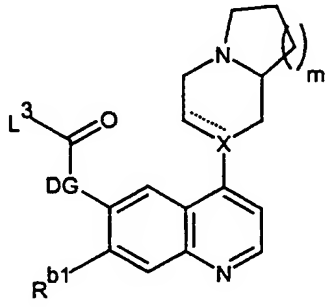
in which R^a is as defined in formula (I), and L^3 is an appropriate leaving group, with a compound of formula (V); or

(e) where L is - Y -C(=O)-DG - in which D is CH and Y is NH, reacting a compound of formula (VI):

$$R^a\text{-}NH_2$$

(VI)

in which R^a is as defined in formula (I) with a compound of formula (VIII):



(VIII)

in which D, G, R^{b1}, X and m are as defined in formula (I) and L^3 is an appropriate leaving group;

and optionally thereafter:

- removing any protecting groups;
- forming a pharmaceutically acceptable salt.

In the reaction of the compounds of formulae (II) and (III), suitable examples of groups L^1 and L^2 include:-

L^1 is COL^a and L^2 is NH_2

L^1 is NH_2 and L^2 is COL^a

in which L^a is an appropriate leaving group.

Suitably one of L^1 and L^2 is an activated carboxylic acid derivative such as an acyl chloride or acid anhydride, and the other is an amine group. Activated compounds of formulae (II) and (III) can also be prepared by reaction of the corresponding carboxylic acid with a coupling agent such as dicyclohexylcarbodiimide, carbonyldiimidazole or diphenylphosphorylazide. Preferably L^1 or L^2 is a group COL^a where L^a is halo particularly chloro.

Compounds of formulae (II) and (III) are typically reacted together in an inert solvent such as dimethylformamide, tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as an alkali metal hydroxide, triethylamine or pyridine.

In process (b) the reaction is conveniently effected in an organic solvent such as dichloromethane.

In process (c) the urea forming agent can be carbonyl diimidazole, triphosgene or phosgene, and carried out in an inert organic solvent such as dimethylformamide, tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

In process (d) the leaving group L^3 is halogen e.g. chloro group and the reaction may be carried out in an inert organic solvent such as tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

In process (e) the leaving group L^3 is halogen e.g. chloro group and the reaction may be carried out in an inert organic solvent such as tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

Intermediate compounds of formula (II) to (VIII) are commercially available, may be prepared according to literature methods or by analogous methods to those described herein.

It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. These groups can be removed by conventional procedures well known in the art.

Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection is achieved using standard conditions.

The involvement of serotonin receptors in a number of pharmacological effects has been reviewed by R. A. Glennon in "Serotonin Receptors: Clinical Implications", Neuroscience and Behavioural Reviews, 1990, 14, 35 and by L.O.Wilkinson and C.T. Dourish in "Serotonin Receptor Subtypes : Basic and Clinical Aspects" S. Peroutka Ed., John Wiley and Sons, New York, 1991 p.147.

Serotonin (5-hydroxytryptamine; 5-HT) receptors have been implicated in a number of pharmacological effects including mood disorders including depression, seasonal affective disorder and dysthymia, anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnesic disorders and age-associated memory impairment; disorders of eating behaviours, including anorexia nervosa and bulimia nervosa, sleep disorders (including disturbances of Circadian rhythm), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders. Serotonin receptor ligands have been shown to be of use in the treatment of emesis and nausea and may also be of use in endocrine disorders such as hyperlactinaemia, vasospasm (particularly in the cerebral vasculature), cerebellar ataxia and hypertension, as well as disorders of the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction and hypothermia.

Ligands with high affinity for the 5-HT_1 receptors are well recognised as having therapeutic utility for the treatment of the above conditions. For example: WO 95/31988 refers to the use of a 5-HT_{1D} receptor antagonist in conjunction with a 5-HT_{1A} receptor antagonist to treat CNS (central nervous system), endocrine and GI (gastrointestinal) disorders; K. Rasmussen (Annual Reports in Medicinal Chemistry, (1995) 30, 1) describes the utility of 5-HT_{1A} receptor agonists and partial agonists in the treatment of various CNS disorders; P. Trouillas (Progress in Brain Research, C.I. de Zeeuw, P. Stara and J. Voogd, Eds. 1997, 144, 589) and G. Maura (J. Neurochemistry, 1996, 66, 202) propose that administration of agonist ligands selective for the 5-HT_{1A} receptor or for both 5-HT_{1A} and 5-HT_{1D} receptors should provide effective treatment for human cerebellar ataxias.

The present invention also provides a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such

treatment of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof.

In particular the invention provides a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

The affinities of the compounds of this invention for the 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors can be determined by the following radioligand binding assay. HEK 293 cells expressing 5-HT_{1A} receptors (4 x 10^7/ml) are homogenised in Tris buffer and stored in 1ml aliquots. CHO cells expressing 5-HT_{1B} receptors (4 x 10^7 cells/ml) are homogenised in Tris buffer and stored in 1.5 ml aliquots. CHO cells expressing 5-HT_{1D} receptors (0.563 x 10^8/ml) are homogenised in Tris buffer and stored in 1 ml aliquots. 0.4 ml of a cell suspension is incubated with [^{3}H]-5-HT (4nM) for 5-$HT_{1B/1D}$ receptors and [^{3}H]-8-OH DPAT (1nM) for 5-HT_{1A} receptors in Tris Mg HCl buffer (pH 7.7) and test drug, at 37°C for 45 minutes. Each test drug is tested at 10 concentrations (0.01 mM to 0.3 nM final concentration), with non-specific binding defined using 0.01 mM 5-HT. The total assay volume is 0.5 ml. Incubation is stopped by rapid filtration using a Packard Filtermate (filters pre-soaked in 0.3% polyethylenimine) and radioactivity measured by Topcount scintillation counting. pKi values are calculated from the IC_{50} generated by an iterative least squares curve fitting programme.

The intrinsic activity of the compounds of this invention can be determined according to the following procedure. HEK293 cell membranes stably expressing human 5-HT_{1A} receptors and CHO cell membranes stably expressing human 5-HT_{1B} receptors are homogenised in HEPES/EDTA buffer and stored in 1ml aliquots, and [^{35}S]GTPγS binding studies are carried out essentially as described by Lazareno *et al.*, (Life Sci., 1993, **52**, 449) with some minor modifications. Membranes from 10^6 cells are pre-incubated at 30°C for 30 min in 20 mM HEPES buffer (pH 7.4) in the presence of $MgCl_2$ (3 mM), NaCl (100 mM), GDP (10 μM) and ascorbate (0.2 mM), with or without compounds. The reaction is started by the addition of 10 μl of [^{35}S]GTPγS (100 pM, assay concentration) followed by a further 30 minutes incubation at 30°C. Non-specific binding was determined using non-radiolabelled GTPγS (20 μM) added prior to the membranes. The reaction is terminated by rapid filtration through Whatman GF/B grade filters followed by 5 x 1 ml washes with ice cold HEPES (20 mM) /$MgCl_2$ (3 mM) buffer. Radioactivity is measured using liquid scintillation spectrometry. This procedure is hereafter referred to as the [^{35}S]GTPγS functional assay.

The compounds of formula (I) show high affinity for the 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors. It has been found, using the [^{35}S]GTPγS functional assay, that certain compounds of formula (I) show varying levels of intrinsic efficacy, which is defined by a scale ranging from 1.0 to 0 (1 defines the maximum response elicited by the agonist 5-HT, 0 defines antagonism). The difficulties in describing intrinsic activity of drugs acting at G protein coupled receptors is recognised in the art (Hoyer and Boddeke, Trends in Pharmacological Sciences, July 1993, [Vol. 14], page 270-275). We believe that however these ligands are classified according to this functional assay, the compounds of this invention will be useful antidepressants *in vivo*. It is believed that the preferred compounds of this invention will display 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} antagonist activity *in vivo* and that such compounds will have a rapid onset of action. A rapid onset of action is particularly advantageous for antidepressant compounds: by 'rapid onset of action' we mean that a therapeutic response is seen within 7 days from first administration of the compound, as opposed to a period of about 21 days or more which is typical of SSRI's, tricyclic antidepressants and buspirone.

Compounds of formula (I) which have an intrinsic activity of 0.5 or less in the [^{35}S]GTPγS functional assay are particularly preferred, as these compounds are more likely to be full antagonists *in vivo*. As disclosed in WO 95/31988, the simultaneous antagonism of pre-synaptic 5-$HT_{1A/1B/1D}$ receptors will result in increased release of 5HT *in vivo* and this will improve 5-HT neurotransmission.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, a selective serotonin reuptake inhibitor (SSRI) antidepressant.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants,

disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

(S)-(-)-6-Nitro-4-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinoline (D1)

A stirred solution of 4-chloro-6-nitroquinoline (*J. Org. Chem.* 1944, **9**, 302) (750 mg, 3.69 mmole) in toluene was treated with (S)-(-)-octahydropyrrolo[1,2-*a*]pyrazine (*J. Med. Chem.*, 1993, **36**, 2311) (500 mg, 3.97 mmole) and heated at reflux for 48 h, then cooled and concentrated to dryness *in vacuo*. Silica gel chromatography (DCM/MeOH 19:1) gave the title compound as a yellow oil (620 mg, 56%).
^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.98 (d, 1H), 8.84 (d, 1H), 8.41 (dd, 1H), 8.14 (d, 1H), 6.98 (d, 1H), 3.74-3.56 (m, 2H), 3.26-3.17 (m, 3H), 2.88 (t, 1H), 2.70 (td, 1H), 2.55-2.45 (m, 1H), 2.43-2.32 (m, 1H), 2.03-1.80 (m, 3H), 1.65-1.51 (m, 1H).
MS: m/z (MH) = 299.

Description 2

(S)-(-)-6-Amino-4-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinoline (D2)

A stirred solution of (S)-(-)-6-nitro-4-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinoline (D1, 600 mg, 2.01 mmole) in EtOH (36 ml) and water (18 ml) was treated with iron powder (0.72 g, 12.9 mmole) and NH_4Cl (86 mg, 1.6 mmole) and heated at reflux for 4 h. After cooling, the mixture was filtered through kieselguhr and the filtrate concentrated to dryness *in vacuo*. The residue was taken up into DCM (50 ml) and washed with water. The organic phase was dried ($MgSO_4$), filtered and concentrated to dryness *in vacuo* giving the title compound as a yellow crystalline solid (300 mg, 56%).
^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.50 (d, 1H), 7.90 (d, 1H), 7.14-7.10 (m, 2H), 6.82 (d, 1H), 3.99 (br. s, 2H), 3.65-3.50 (m, 2H), 3.22-3.17 (m, 2H), 3.05 (td, 1H), 2.72 (t, 1H), 2.62 (td, 1H), 2.50-2.40 (m, 1H), 2.40-2.29 (m, 1H), 2.01-1.80 (m, 3H), 1.62-1.47 (m, 1H).
MS: m/z (MH) = 269.

Description 3

1-Benzyl-5-nitroindoline (D3)

To a stirred solution of 5-nitroindoline (50 g, 0.30 mole) in acetone (500 ml) was added anhydrous K_2CO_3 (55.3 g, 0.40 mole), followed by dropwise addition of benzyl bromide (42 ml, 0.35 mole) over 45 minutes. The mixture was stirred at room temperature for 24 h. Further benzyl bromide (10.0 ml, 0.08 mole) and K_2CO_3 (12.0 g, 0.09 mole) were added and the mixture heated at reflux for 3 days. On cooling, the mixture was filtered and the filtrate evaporated *in vacuo* to a dark red oil. Trituration with hexane afforded the title compound as an orange crystalline solid (79.0 g, 100%).
^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.05 (d, 1H), 7.91 (s, 1H), 7.40-7.25 (m, 5H), 6.35 (d, 1H), 4.35 (s, 2H), 3.63 (t, 2H), 3.09 (t, 2H). MS: m/z (MH) = 255.

Description 4

5-Amino-1-benzylindoline (D4)

A mixture of 1-benzyl-5-nitroindoline (D3, 20.0 g, 0.08 mole), tin(II)chloride (60.0 g, 0.32 mole) and conc. HCl (40 ml) in MeOH (400 ml) was heated at reflux for 16 h. On cooling, the mixture was evaporated *in vacuo* to a red oil, which was partitioned between DCM and water, basified with 40% NaOH solution and the insoluble tin residues removed by filtration. The filtrate was extracted with DCM (2x), dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a dark green oil (10.5 g, 60%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.41-7.23 (m, 5H), 6.58 (s, 1H), 6.45 (dd, 1H), 6.37 (d, 1H), 4.13 (s, 2H), 3.31 (br. s, 2H), 3.18 (t, 2H), 2.87 (t, 2H). MS: m/z (MH) = 225.

Description 5

Diethyl (1-benzylindolin-5-ylamino)methylenemalonate (D5)

Diethyl ethoxymethylenemalonate (9.45 ml, 0.05 mole) was added to a solution of 5-amino-1-benzylindoline (D4, 10.5 g, 0.05 mole) in toluene (500 ml) and the mixture heated at reflux under argon for 1.5 h. On cooling, the solvent was removed *in vacuo* to give a brown oil (19.6 g). Purification by silica gel chromatography eluting with hexane:EtOAc (70:30), afforded the title compound as a yellow crystalline solid (14.3 g, 77%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.42 (d, 1H), 7.38-7.28 (m, 5H), 6.93 (s, 1H), 6.83 (dd, 1H), 6.44 (d, 2H), 4.33-4.17 (m, 6H), 3.36 (t, 2H), 2.99 (t, 2H), 1.40-1.25 (m, 6H). MS: m/z (MH) = 395.

Description 6

Ethyl 1-benzyl-8-chloro-2,3-dihydropyrrolo[2,3-*g*]quinolin-7-ylcarboxylate (D6)

Diethyl (1-benzylindolin-5-ylamino)methylenemalonate (D5, 10.0 g, 25.3 mmole) in phosphorous oxychloride (40 ml) was heated at reflux under argon for 2.5 h. On cooling, the mixture was concentrated *in vacuo* and the residual oil treated with 10% aqueous Na_2CO_3 solution until basic. Extraction with DCM afforded a red gum, which was purified using silica gel chromatography, eluting with hexane:EtOAc (70:30), to afford the title compound as a yellow crystalline solid (6.3 g, 68%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.81 (s, 1H), 7.69 (s, 1H), 7.40-7.27 (m, 5H), 7.02 (s, 1H), 4.51 (s, 2H), 4.46 (q, 2H), 3.59 (t, 2H), 3.24 (t, 2H), 1.44 (t, 3H). MS: m/z (MH) = 367.

Description 7

(S)-(-)-Ethyl 1-benzyl-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinolin-7-ylcarboxylate (D7)

To a mixture of ethyl 1-benzyl-8-chloro-2,3-dihydropyrrolo[2,3-*g*]quinolin-7-ylcarboxylate (D6, 4.0 g, 10.9 mmole) and (S)-(-)-octahydropyrrolo[1,2-*a*]pyrazine (*J. Med. Chem.*, 1993, 36, 2311) (6.0 g, 47.6 mmole) in DMF (60 ml) was added triethylamine (20 ml) and the mixture heated at 90°C under argon for 40 h. On cooling, the DMF was removed *in vacuo* and the residue purified by silica gel chromatography, eluting with EtOAc:MeOH (19:1), to afford the title compound as a dark orange crystalline solid (4.5 g, 90%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.56 (s, 1H), 7.67 (s, 1H), 7.41-7.26 (m, 5H), 6.79 (s, 1H), 4.49-4.37 (m, 4H), 3.60 (t, 2H), 3.35-3.06 (m, 6H), 2.99-2.89 (m, 2H), 2.26-2.09 (m, 2H), 1.86-1.64 (m, 4H), 1.43-1.37 (m, 4H). MS: m/z (MH) = 457.

Description 8

(S)-(-)-1-Benzyl-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinolin-7-ylcarboxylic acid (D8)

(S)-(-)-Ethyl 1-benzyl-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinolin-7-ylcarboxylate (D7, 1.8 g, 4.1 mmole) in EtOH (36 ml) was treated with a solution of NaOH (0.35 g, 8.8 mmole) in water (7 ml) and the mixture heated at reflux for 16h. The EtOH was removed *in vacuo*, the residue diluted with water and treated with 2M HCl solution to pH7. The water was removed *in vacuo* giving the title compound as a yellow solid (1.7 g, 100%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.69 (s, 1H), 7.85(s, 1H), 7.41-7.27 (m, 5H), 6.50 (s, 1H), 4.47 (s, 2H), 4.10-3.78 (br. s, 2H), 3.70 (t, 2H), 3.66-3.28 (br. m, 3H), 3.27-3.03 (br. m, 3H), 2.85-2.38 (br.s, 3H), 2.13 (br. s, 1H), 1.97 (br. s, 1H), 1.86 (br. s, 2H). Acid proton not observed. MS: m/z (M-H) = 427.

Description 9

(S)-(-)-1-Benzyl-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D9)

(S)-(-)-1-Benzyl-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinolin-7-ylcarboxylic acid (D8, 1.7g, 4.0 mmole) in Dowtherm A (200 ml) was heated at reflux for 30 minutes. On cooling, the mixture was poured into hexane (600 ml) and extracted into 2M HCl solution (3x). The acidic extracts were combined and basified with K_2CO_3, then extracted with EtOAc (3x). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as an orange oil (1.4 g, 90%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.41 (d, 1H), 7.69(s, 1H), 7.42-7.26 (m, 5H), 6.75 (d, 1H), 6.63 (s, 1H), 4.40 (s, 2H), 3.59-3.47 (m, 3H), 3.36 (dd, 1H), 3.22-2.88 (m, 5H), 2.58 (t, 1H), 2.37 (dt, 1H), 2.24-2.17 (m, 2H), 1.95-1.73 (m, 3H), 1.47-1.34 (m, 1H).
MS: m/z (MH) = 385.

Description 10

(S)-(-)-2,3-Dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10)

(S)-(-)-1-Benzyl-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D9, 1.4 g, 3.6 mmole) in EtOH (100 ml) and 2M HCl solution (4 ml) was hydrogenated over 10% palladium on charcoal at 50 psi and room temperature for 32 h. The mixture was then filtered through kieselguhr and concentrated *in vacuo*. The residue was partitioned between DCM and 10% aqueous Na_2CO_3 solution and the organic phase separated, dried ($MgSO_4$) and concentrated to dryness *in vacuo*, giving the title compound as an orange solid (0.66 g, 62%).
^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.45 (d, 1H), 7.72(s, 1H), 6.98 (s, 1H), 6.79 (d, 1H), 4.13 (br. s, 1H), 3.68 (t, 2H), 3.58 (dd, 1H), 3.47 (dd, 1H), 3.25-3.15 (m, 3H), 2.99 (dt, 1H), 2.67-2.56 (m, 2H), 2.39-2.24 (m, 2H), 1.97-1.45 (m, 5H). MS: m/z (MH) = 295.

Description 11

5-Carboxynaphth-1-ylboronic acid (D11)

A stirred solution of 5-bromo-1-naphthoic acid (*Bull. Soc. Chim. Fr.*, 1968, 7, 2957) (22.3 g, 0.089 mole) in dry THF (1000 ml) at -60°C under argon was treated dropwise over 15 minutes with 1.6M n-butyllithium in hexane (125 ml, 0.20 mole). The initial brown solution gave a beige precipitate as the first equivalent was added, which redissolved on addition of the second equivalent. The resulting solution was stirred at -60°C for 40 minutes, then triisopropylborate (51 ml, 0.22 mole) was added, and the mixture stirred at -60°C for a further 1 h, before warming gradually to -10°C. Saturated aqueous NH_4Cl solution was added (300 ml), followed by water (400 ml) and then 5M HCl solution (200 ml). The resulting mixture was concentrated *in vacuo* to approx. 1000 ml volume, then basified by addition of 40% aqueous NaOH solution and washed with EtOAc. The aqueous was added to excess 5M HCl solution and the solid which precipitated out was filtered off, washed with water and dried to afford a white solid (9.67 g), which contained approx. 50% of the title compound together with 1-naphthoic acid.

Description 12

2,6-Dimethyl-4-iodopyridine (D12)

A stirred solution of 4-chloro-2,6-dimethylpyridine (*Chem. Abs.* 1952, 46, 4541) (2.6 g, 18 mmole) in 2-butanone (250 ml) was treated with sodium iodide (17.6 g, 120 mmole) and 4-toluenesulphonic acid (3.4 g, 18 mmole) and the mixture heated at reflux under argon for 72 h. The reaction mixture was cooled, then concentrated *in vacuo* and the residue was treated with water (200 ml) and extracted with EtOAc. The extract was washed with aqueous sodium thiosulphate solution, then dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a white solid, which was converted to its hydrochloride salt as a white solid from acetone (3.44 g, 69%).

^1H NMR (free base) (250 MHz, $CDCl_3$) δ (ppm): 7.37 (s, 2H), 2.46 (s, 6H)

MS: m/z (MH) = 234.

Description 13

5-(2,6-Dimethylpyridin-4-yl)-1-naphthoic acid (D13)

A stirred suspension of 2,6-dimethyl-4-iodopyridine (D12, 1.66 g, 7.1 mmole) and 5-carboxynaphth-1-ylboronic acid (D11, 1.54 g, 7.1 mmole) in 1,2-dimethoxyethane (60 ml) and water (15 ml) containing Na_2CO_3 (2.27 g, 21.4 mmole) was flushed with argon for 20 minutes. Tetrakis(triphenylphosphine)palladium (0) (0.41 g, 0.36 mmole) was added and the mixture heated at reflux under argon for 18 h. The 1,2-dimethoxyethane was removed *in vacuo* and the residue diluted with 2M NaOH solution and washed with EtOAc. The aqueous phase was acidified to pH1 with conc. HCl and washed with EtOAc, then adjusted to pH5 with K_2CO_3 and extracted with DCM (3x). The DCM extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo*, giving the title compound as a white solid (1.38 g, 70%).

^1H NMR (250 MHz, d^6DMSO) δ (ppm): 8.75 (d, 1H), 7.99 (dd, 1H), 7.80 (d, 1H), 7.60-7.52 (m, 1H), 7.50-7.32 (m, 2H), 7.00 (s, 2H), 2.36 (s, 6H). Acid proton not observed.

MS: m/z (M-H) = 276.

Description 14

5-(2,6-Dimethylpyridin-4-yl)-1-naphthoyl chloride (D14)

A suspension of 5-(2,6-dimethyl-pyridin-4-yl)-1-naphthoic acid (D13, 200 mg, 0.72 mmole) in DCM (10 ml) was treated with oxalyl chloride (0.13 ml, 1.49 mmole) and stirred at room temperature for 16 h, then concentrated to dryness *in vacuo* giving the title compound as a cream coloured solid, which was used directly in the next step.

Description 15

5-(2,6-Dimethylpyridin-4-yl)naphth-1-yl isocyanate (D15)

A suspension of 5-(2,6-dimethylpyridin-4-yl)-1-naphthoic acid (D13, 250 mg, 0.91 mmole) in DCM (10 ml) was treated with oxalyl chloride (0.16 ml, 1.81 mmole) and stirred at room temperature for 18 h, then concentrated to dryness *in vacuo*. The residue was redissolved in DCM (20 ml) and shaken quickly with ice-cold saturated aqueous $NaHCO_3$ solution (10 ml). The organic phase was immediately separated and added to a stirred solution of sodium azide (111 mg, 1.71 mmole) and tetrabutylammonium iodide (22 mg) in water (10 ml) at 5°C. The mixture was stirred vigorously at 0-5°C for 1.5 h, then diluted with water (10 ml) and the DCM layer separated, dried (Na_2SO_4) and concentrated cautiously under *vacuum*, at room temperature, to approx. 10 ml volume. This solution was then treated with toluene (10 ml) and heated at reflux under argon for 1.5 h. The reaction mixture was allowed to cool and the isocyanate solution used directly in the next step.

Description 16

5-(5-Methylpyridin-2-yl)-1-naphthoic acid (D16)

The title compound was prepared from 2-iodo-5-methylpyridine and 5-carboxynaphth-1-ylboronic acid (D11) using a similar procedure to Description 13, as a beige solid (64%). ^{1}H NMR (250MHz, d^{6}DMSO) δ (ppm): 13.3 (br s, 1H), 8.94 (d, 1H), 8.55 (s, 1H), 8.20 (d, 1H), 7.97 (d, 1H), 7.89 7.70 (m, 2H), 7.70–7.50 (m, 2H), 7.45 (d, 1H), 2.60 (s, 3H).

Description 17

5-(6-Methylpyridin-2-yl)-1-naphthoic acid (D17)

The title compound was prepared from 2-bromo-6-methylpyridine and 5-carboxynaphth-1-ylboronic acid (D11) using a similar procedure to Description 13, as a beige solid (46%). ^{1}H NMR (250MHz, d^{6}DMSO) δ (ppm): 8.90 (d, 1H), 8.13 (d, 1H), 8.06 (dd, 1H), 7.84 (t, 1H), 7.67 (t, 1H), 7.62-7.46 (m, 2H), 7.41 (d, 1H), 7.32 (d, 1H), 2.55 (s, 3H). Acid proton not observed.

Description 18

4-Bromo-N-propargyl-1-naphthylcarboxamide (D18)

A stirred suspension of 4-bromo-1-naphthoic acid (*J. Chem. Soc.* 1958, 1426) (3.30 g, 13 mmole) in DCM (180 ml) was treated with oxalyl chloride (3.4 ml, 39 mmole). After 5 h the mixture was concentrated to dryness *in vacuo* and the residue dissolved in DCM (120 ml)

and treated with a solution of propargylamine (0.83 g, 15 mmole) and triethylamine (2 ml, 15 mmole) in DCM (50 ml) over 30 minutes. The mixture was stirred overnight at room temperature, then washed successively with 2M HCl solution (50 ml), 20% aqueous K_2CO_3 solution (2 x 50 ml) and brine (50 ml), dried (Na_2SO_4) and concentrated to dryness *in vacuo*. The residue was triturated in Et_2O/n-hexane to afford the title compound as a cream powder (2.62g, 70%).

^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.30 (dd, 2H), 7.78 (d, 1H), 7.64 (m, 2H), 7.43 (d, 1H), 6.21 (s, 1H), 4.32 (q, 2H), 2.31 (t, 1H).

Description 19

1-Bromo-4-(5-methyloxazol-2-yl)naphthalene (D19)

A stirred mixture of 4-bromo-N-propargyl-1-naphthylcarboxamide (D18, 2.60 g, 9.0 mmole) and mercuric acetate (0.02 g, 0.06 mmole) in glacial acetic acid (40 ml) was heated at reflux for 3 h. The cooled mixture was concentrated to dryness *in vacuo* and the residue dissolved in EtOAc (100 ml) and washed successively with 20% aqueous K_2CO_3 solution (2 x 25 ml), water (50ml) and brine (25 ml), dried (Na_2SO_4) and concentrated to dryness *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with DCM, to afford the title compound as a cream powder (2.03 g, 78%).

^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 9.32 (m, 1H), 8.34 (m, 1H), 7.97 (d, 1H), 7.83 (d, 1H), 7.65 (m, 2H), 6.99 (s, 1H), 2.46 (s, 3H).

Description 20

1-Cyano-4-(5-methyloxazol-2-yl)naphthalene (D20)

1-Bromo-4-(5-methyloxazol-2-yl)naphthalene (D19, 2.00 g, 6.9 mmole), copper (I) cyanide (1.11 g, 12.4 mmole) and N-methylpyrrolidinone (20 ml) were stirred at 160°C under argon for 3 h. The cooled mixture was poured into water (200 ml) and EtOAc (150 ml) and to the resultant suspension was added KCN (2.00 g, 30 mmole). After stirring at room temperature for 1.5 h, the layers were separated and the aqueous extracted with EtOAc (2 x 50 ml). The combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated to dryness *in vacuo*. The residue was triturated in Et_2O/n-hexane to afford the title compound as a pale buff coloured solid (1.24 g, 76%).

^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 9.46 (q, 1H), 8.31 (q, 1H), 8.18 (d, 1H), 7.96 (d, 1H), 7.77 (q, 2H), 7.03 (s, 1H), 2.49 (s, 3H).

Description 21

4-(5-Methyloxazol-2-yl)-1-naphthoic acid (D21)

1-Cyano-4-(5-methyloxazol-2-yl)naphthalene (D20, 1.00 g, 4.0 mmole), KOH (2.24 g, 40.0 mmole), PrOH (70 ml) and water (10 ml) were stirred at reflux for 48 h. The cooled mixture was concentrated to dryness *in vacuo* and the residue partitioned between EtOAc (50 ml) and water (70 ml). After stirring for 15 minutes the mixture was filtered and the aqueous separated, washed with EtOAc (25 ml) and acidified to pH 1 with 5M HCl solution. The precipitate was collected, washed with water and dried *in vacuo* to afford the title compound as a colourless solid (0.64 g, 59%).

^{1}H NMR (250 MHz, d^6-DMSO) δ (ppm): 13.46 (s, 1H), 9.39 (m, 1H), 8.91 (m, 1H), 8.20 (s, 2H), 7.75 (m, 2H), 7.22 (s, 1H), 2.47 (s, 3H).

Description 22

5-(2,5-Dimethylpyridin-4-yl)-1-naphthoic acid (D22)

The title compound was prepared from 4-bromo-2,5-dimethylpyridine and 5-carboxynaphth-1-ylboronic acid (D11) using a similar procedure to Description 13, as a white solid (47%).

^{1}H NMR (250MHz, d^{6}DMSO) δ (ppm): 13.3 (br s, 1H), 8.90 (d, 1H), 8.45 (s, 1H), 8.17-8.10 (m, 1H), 7.75-7.66 (m, 1H), 7.57-7.47 (m, 2H), 7.41 (d, 1H), 7.12 (s, 1H), 2.50 (s, 3H), 1.86 (s, 3H).

Description 23

5-(3-Methylpyridin-2-yl)-1-naphthoic acid (D23)

The title compound was prepared from 2-bromo-3-methylpyridine and 5-carboxynaphth-1-ylboronic acid (D11) using a similar procedure to Description 13, as beige solid (46%).

^{1}H NMR (250MHz, d^{6}DMSO) δ (ppm): 8.92 (d, 1H), 8.56 (dd, 1H), 8.15 (dd, 1H), 7.83 (d, 1H), 7.74 (dd, 1H), 7.55-7.40 (m, 4H), 2.00 (s, 3H). Acid proton not observed.

Description 24

5-Bromo-N-propargyl-1-naphthylcarboxamide (D24)

The title compound was prepared from 5-bromo-1-naphthoic acid (*Bull. Soc. Chim. Fr.*, 1968, 7, 2957) using a similar procedure to Description 18, as a pale yellow solid (5.48 g, 70%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 8.35 (d, 1H), 8.28 (d, 1H), 7.82 (d, 1H), 7.66 (d, 1H), 7.58 (t, 1H), 7.38 (t, 1H), 6.24 (s, 1H), 4.33 (q, 2H), 2.31 (t, 1H).

Description 25

1-Bromo-5-(5-methyloxazol-2-yl)naphthalene (D25)

The title compound was prepared from 5-bromo-N-propargyl-1-naphthylcarboxamide (D24, 5.45 g, 18.9 mmole) using a similar procedure to Description 19, as a pale yellow solid (2.80g, 50%).

^{1}H NMR (250 MHz; $CDCl_3$) δ (ppm): 9.30 (d, 1H), 8.38 (d, 1H), 8.18 (d, 1H), 7.84 (d, 1H), 7.64 (t, 1H), 7.45 (t, 1H), 6.99 (s, 1H), 2.46 (s, 3H).

Description 26

Diethyl 5-(2-methyloxazol-2-yl)-1-naphthyl malonate (D26)

A stirred solution of diethylmalonate (3.42 g, 21.4 mmole) in dry dioxane (100 ml) was treated, portionwise, with sodium hydride (0.86 g, 60% dispersion in oil). After 15 minutes copper (I) bromide (3.07 g, 21.4 mmole) and 1-bromo-5-(5-methyloxazol-2-yl)naphthalene (D25, 3.09 g, 10.7 mmole) were successively added. The mixture was then heated at reflux under argon for 8 h. The cooled mixture was filtered through Celite (Diatomaceous Earth) and concentrated to dryness *in vacuo*. The residue was dissolved in EtOAc (100 ml) and washed successively with 2M HCl solution (2 x 30 ml), water (30 ml) and brine (30 ml), dried (Na_2SO_4) and concentrated to dryness *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with DCM-MeOH (0-2% MeOH gradient elution), to afford the title compound as a yellow oil (1.70 g, 43%).

^{1}H NMR (250 MHz, d^{6}DMSO) δ(ppm): 9.28 (d, 1H), 8.18 (m, 2H), 7.70 (m, 2H), 7.55 (dd, 1H), 7.16 (s, 1H), 4.26-4.07 (m, 5H), 2.45 (s, 3H), 1.17 (t, 6H).

Description 27

5-(5-Methyloxazol-2-yl)-1-naphthylacetic acid (D27)

Diethyl 5-(5-methyloxazol-2-yl)-1-naphthyl malonate (D26, 1.70 g, 4.6 mmol), glacial acetic acid (10 ml) and conc. HCl (10 ml) were stirred at reflux for 7 h. The cooled mixture was concentrated to dryness *in vacuo*, the residue triturated in water (25 ml) and the solid filtered off and dried *in vacuo*, giving the title compound as a pale grey powder (0.90 g, 73%).

^{1}H NMR (250 MHz, d^6 DMSO) δ (ppm): 9.06 (d, 1H), 8.02 (d, 2H), 7.58 - 7.40 (m, 3H), 7.02 (s, 1H), 4.03 (s, 2H), 2.33 (s, 3H). Acid proton not observed.

Description 28

Ethyl 5-bromo-1-naphthoate (D28)

A stirred suspension of 5-bromo-1-naphthoic acid (*Bull. Soc. Chim. Fr.*, 1968, 7, 2957) (10.0 g, 0.040 mole) in EtOH (150 ml) was treated with conc. H_2SO_4 (7 ml) and heated at reflux

for 24 h. On cooling, the EtOH was removed *in vacuo* and the residue partitioned between EtOAc and 10% aqueous Na_2CO_3 solution. The organic phase was separated, the aqueous extracted with more EtOAc and the organics combined, dried (Na_2SO_4) and concentrated to dryness *in vacuo*, affording the title compound as a white solid (10.14 g 91%).
^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.88 (d, 1H), 8.49 (d, 1H), 8.20 (dd, 1H), 7.84 (dd, 1H), 7.61 (dd, 1H), 7.43 (dd, 1H), 4.48 (q, 2H), 1.46 (t, 3H).

Description 29

Ethyl 5-acetyl-1-naphthoate (D29)

A stirred solution of ethyl 5-bromo-1-naphthoate (D28, 8.98 g, 32.2 mmole) and tributyl(1-ethoxyvinyl)tin (13.9 g, 38.5 mmole) in dry 1,4-dioxane was degassed by bubbling with argon for 20 min. Bis(triphenylphosphine)palladium (II) dichloride was added and the mixture heated at reflux under argon for 18 h. On cooling, 2M HCl solution (20 ml) and water (50 ml) were added and this mixture stirred vigorously at room temperature for 4 h. The mixture was then concentrated *in vacuo* and the residue partitioned between water and EtOAc and filtered through kieselguhr to remove catalyst residues. The organic phase was separated, dried ($MgSO_4$) and concentrated to dryness *in vacuo* giving a pale yellow crystalline solid, which was broken up and washed thoroughly with 60-80 petrol to remove tin residues, then filtered off and dried under vacuum, giving the title compound as a pale yellow solid (5.31 g, 68%).
^1H NMR (250MHz, $CDCl_3$) δ (ppm): 9.10 (d, 1H), 8.89 (d, 1H), 8.20 (dd, 1H), 7.97 (dd, 1H), 7.66-7.57 (m, 2H), 4.48 (q, 2H), 2.76 (s, 3H), 1.47 (t, 3H). MS: m/z (MH) = 243.

Description 30

Ethyl 5-bromoacetyl-1-naphthoate (D30)

A stirred solution of ethyl 5-acetyl-1-naphthoate (D29, 4.80 g, 17.2 mmole) in a mixture of DCM (80 ml) and MeOH (40 ml) was treated with benzyltrimethylammonium tribromide (7.38 g, 18.9 mmole) and stirred at room temperature for 18 h. The solvents were then removed *in vacuo* and the residue partitioned between DCM and water. The organic phase was separated, dried (Na_2SO_4) and concentrated to dryness *in vacuo* affording the title compound as an orange-brown solid (5.52 g, 100%).
^1H NMR (250MHz, $CDCl_3$) δ (ppm): 9.16 (d, 1H), 8.75 (d, 1H), 8.23 (dd, 1H), 7.95 (dd, 1H), 7.68-7.61 (m, 2H), 4.58 (s, 2H), 4.49 (q, 2H), 1.47 (s, 3H).

Description 31

Ethyl 5-aminoacetyl-1-naphthoate hydrochloride (D31)

Ethyl 5-bromoacetyl-1-naphthoate (D30, 3.50 g, 10.9 mmole) was dissolved in DCM (40 ml) and cooled in an ice bath to ~5°C. This solution was treated with tetrabutylammonium iodide (0.20 g, 0.54 mmole) and a solution of sodium azide (1.06 g, 16.3 mmole) in water (8 ml) and stirred vigorously for 3 h, while warming to room temperature. Water (30 ml) was added and the organic phase separated, dried (Na_2SO_4) and concentrated carefully *in vacuo* to approx. 20 ml volume. EtOH (40 ml) was added and the mixture concentrated *in vacuo* to approx. 40 ml (to remove the remaining DCM). This solution was diluted with EtOH (200 ml), treated with conc. HCl (5 ml) and hydrogenated over 10% palladium on charcoal at room temperature and pressure for 48 h. The mixture was then filtered through kieselguhr and concentrated to dryness *in vacuo*, affording the title compound as a white solid (2.26 g, 71%).

^{1}H NMR (250MHz, d^{6}DMSO) δ (ppm): 8.98 (d, 1H), 8.84 (d, 1H), 8.45 (br s, 3H), 8.32 (dd, 1H), 8.19 (dd, 1H), 7.86-7.77 (m, 2H), 4.70 (s, 2H), 4.44 (q, 2H), 1.40 (t, 3H).

MS: m/z (MH) = 258.

Description 32

Ethyl 5-acetamidoacetyl-1-naphthoate (D32)

Ethyl 5-aminoacetyl-1-naphthoate hydrochloride (D31, 2.26 g, 7.70 mmole) was suspended with stirring in DCM (60 ml) and treated with triethylamine (1.2 ml, 8.50 mmole) and acetic anhydride (0.86 g, 8.5 mmole). After 18 h, the mixture was concentrated to dryness *in vacuo* and the residue partitioned between EtOAc and 10% aqueous Na_2CO_3 solution. The organic phase was separated, dried (Na_2SO_4), concentrated to dryness *in vacuo* and purified by silica gel chromatography, eluting with EtOAc, to afford the title compound as a white solid (1.73 g, 60%).

^{1}H NMR (250MHz, $CDCl_3$) δ (ppm): 9.17 (d, 1H), 8.90 (d, 1H), 8.23 (dd, 1H), 8.02 (dd, 1H), 7.69-7.62 (m, 2H), 6.57 (br s, 1H), 4.82 (d, 2H), 4.49 (q, 2H), 2.15 (s, 3H), 1.47 (t, 3H).

MS: m/z (MH) = 300.

Description 33

Ethyl-(2-methyloxazol-5-yl)-1-naphthoate (D33)

Ethyl 5-acetamidoacetyl-1-naphthoate (D33, 1.71 g, 5.72 mmole) was covered with polyphosphoric acid (~ 48 g) and the resulting viscous mixture was heated with stirring, under argon. On reaching 140°C, the mixture was partially cooled and poured into a beaker of crushed ice (~ 50 ml) with stirring. Water (50 ml) was added and the solution extracted

with EtOAc. The organic phase was separated, dried (Na_2SO_4) and concentrated to dryness *in vacuo* affording a pale yellow solid, which ^{1}H NMR showed to be a mixture of the title compound and 5-(2-methyloxazol-5-yl)-1-naphthoic acid.

Description 34

5-(2-Methyloxazol-5-yl)-1-naphthoic acid (D34)

Ethyl 5-(2-methyloxazol-5-yl)-1-naphthoate (D33, 5.72 mmole) was suspended, with stirring, in a mixture of EtOH (30 ml) and 2M NaOH solution (30 ml) and heated at reflux for 1 h. The mixture was partially cooled and the EtOH removed *in vacuo*. The residue was washed with Et_2O and the aqueous layer was acidified to pH1 with conc. HCl. This was then extracted with EtOAc (3 x 200 ml) and the organic extracts combined, dried (Na_2SO_4) and concentrated to dryness *in vacuo*, affording the title compound as a pale yellow solid (1.19 g, 82% over 2 steps).

^{1}H NMR (250MHz, d^{6}DMSO) δ (ppm): 8.89 (d, 1H), 8.49 (d, 1H), 8.18 (dd, 1H), 7.82 (dd, 1H), 7.76-7.66 (m, 2H), 7.55 (s, 1H), 2.56 (s, 3H). Acid proton not observed.

MS: m/z (M-H) = 252.

Description 35

Ethyl 5-(3-methylisoxazol-5-yl)-1-naphthoate (D35)

A stirred solution of ethyl 5-bromo-1-naphthoate (D28, 2.59 g, 9.3 mmole) and 3-methyl-5-(tributylstannyl)isoxazole (*Tetrahedron*, 1991, **47**, 5111) in dry 1,4-dioxane was degassed by bubbling with argon for 20 minutes. Bis(triphenylphosphine)palladium (II) dichloride was added and the mixture heated at reflux under argon for 24 h. On cooling, the 1,4-dioxane was removed *in vacuo* and the residue partitioned between water and DCM. The organic phase was separated, dried ($MgSO_4$) and concentrated to dryness *in vacuo* giving an orange / brown oil. Purification by silica gel chromatography, eluting with 60-80 petrol:Et_2O (2:1), afforded the title compound as a cream coloured solid (857 mg, 33%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 9.03 (d, 1H), 8.46 (d, 1H), 8.21 (dd, 1H), 7.80 (dd, 1H), 7.66 (dd, 1H), 7.58 (dd, 1H), 6.43 (s, 1H), 4.50 (q, 2H), 2.44 (s, 3H), 1.47 (t, 3H).

MS: m/z (MH) = 282.

Description 36

5-(3-Methylisoxazol-5-yl)-1-naphthoic acid (D36)

The title compound was prepared from ethyl 5-(3-methylisoxazol-5-yl)-1-naphthoate (D35, 815 mg, 2.90 mmole) using a similar procedure to Description 34, as a white solid (638 mg, 87%).
^{1}H NMR (250MHz, d^{6}DMSO) δ (ppm): 13.38 (br s, 1H), 9.00 (d, 1H), 8.40 (d, 1H), 8.21 (dd, 1H), 7.90 (dd, 1H), 7.80-7.69 (m, 2H), 6.90 (s, 1H), 2.38 (s, 3H). MS: m/z (M-H) = 252.

Description 37

(S)-(-)-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D37)

A solution of (S)-(-)-2,3-Dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 588 mg, 2 mmole) in MeOH (15 ml) was treated with $PdCl_2$ (354 mg, 2 mmol) and Et_3N (280 ml, 2 mmole) and heated under reflux for 15 h. The suspension was filtered through Kieselguhr, washing thoroughly with MeOH. The combined methanolic phases were brought to pH 10 with K_2CO_3 and partitioned between water and EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo* giving a brown solid (150 mg, 26%).
^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.68 (d, 1H), 8.39 (s, 1H), 8.03 (s, 1H), 7.48 (dd, 1H), 6.81 (d, 1H), 6.73 (s, 1H), 3.73-3.58 (m, 2H), 3.21-3.03 (m, 3H), 2.78-2.56 (m, 2H), 2.43-2.24 (m, 3H), 1.96-1.79 (m, 3H), 1.55-1.46 (m, 1H). MS: m/z (MH) = 293.

Description 38

5-(6-Methylpyridin-2-yl)-1-naphthoyl chloride (D38)

A suspension of 5-(6-methylpyridin-2-yl)-1-naphthoic acid (D17, 180 mg, 0.68 mmole) in DCM (20 ml) was treated with oxalyl chloride (0.15 ml, 1.8 mmole) and stirred at room temperature for 2 h, then concentrated to dryness *in vacuo* giving the title compound as a cream coloured solid, which was used directly in the next step.

Description 39

7-Bromo-3-trifluoroacetylindole (D39)

A stirred, ice-cooled solution of 7-bromoindole (2.0 g, 10.2 mmole) in DMF (8 ml) was treated, dropwise, with trifluoroacetic anhydride (1.74 ml, 12.2 mmole). This solution was allowed to warm to room temperature over 2 h, then poured into a solution of saturated aqueous $NaHCO_3$ solution. The title compound precipitated as a white solid and was filtered off, washed with water and dried in the vacuum oven at 50°C (2.88 g, 96%).
MS: m/z (M-H) = 290, 292.

Description 40

7-Bromoindole-3-carboxylic acid (D40)

7-Bromo-3-trifluoroacetylindole (D39, 2.88 g, 9.8 mmole) was dissolved in 20% aqueous NaOH solution (30 ml) and heated at reflux for 1 h, then cooled, diluted with water (30 ml) and washed with EtOAc (40 ml). The aqueous phase was separated and acidified to pH1 with 5M aqueous HCl solution. The title compound precipitated as a white solid and was filtered off, washed with water and dried under vacuum (2.10 g, 89%).
MS: m/z (M-H) = 238, 240.

Description 41

Methyl 7-bromo-1-methylindole-3-carboxylate (D41)

A solution of 7-bromoindole-3-carboxylic acid (D40, 2.0 g, 8.3 mmole) in acetone (100 ml) was treated with K_2CO_3 (2.4 g, 17.5 mmole) and MeI (1.1 ml, 17.5 mmole) and heated, under an atmosphere of argon, at 50°C for 40 h. The mixture was then cooled and the solid filtered off, washing with acetone. The filtrate was concentrated to dryness *in vacuo* and the residue taken up in DCM, filtered again, and the filtrate concentrated to dryness *in vacuo*, giving the title compound as a pale yellow solid (1.95 g, 87%).
^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.16 (dd, 1H), 7.72 (s, 1H), 7.41 (dd, 1H), 7.07 (dd, 1H), 4.20 (s, 3H), 3.90 (s, 3H). MS: m/z (MH) = 268, 270.

Description 42

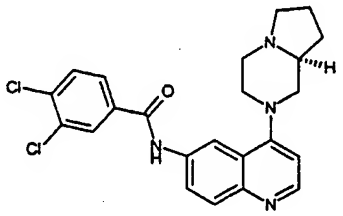
Methyl 1-methyl-7-(6-methylpyridin-2-yl)indole-3-carboxylate (D42)

A stirred solution of methyl 7-bromo-1-methylindole-3-carboxylate (D41, 500 mg, 1.87 mmole) in anhydrous toluene (10 ml) was treated with hexamethylditin (730 mg, 2.24 mmole) and degassed by bubbling with argon for 20 minutes. $Pd(PPh_3)$ was added and the mixture heated at 110°C, under argon, for 18 h. The mixture was then cooled, filtered through Kieselguhr, washing with EtOAc, and the filtrate concentrated *in vacuo* giving the indolyl stannane intermediate as a pale yellow oil. This oil was dissolved with stirring in anhydrous DMF (5 ml), treated with CuI (35 mg, 0.19 mmole) and a solution of 2-bromo-6-methylpyridine (449 mg, 2.61 mmole) in anhydrous DMF (5 ml) and degassed by bubbling with argon. $Pd(PPh_3)_2Cl_2$ was added and the mixture heated at 110°C, under argon, for 18 h. The mixture was partially cooled and the DMF removed *in vacuo*. The residue was purified by silica gel chromatography, eluting with Et_2O, to afford the title compound as a yellow oil (159 mg, 30%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.25 (d, 1H), 7.72-7.66 (m, 2H), 7.37-7.18 (m, 4H), 3.92 (s, 3H), 3.41 (s, 3H), 2.64 (s, 3H). MS: m/z (MH) = 281.

Example 1

(S)-(-)-N-[4-(Octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinolin-6-yl]-3,4-dichlorobenzamide (E1)

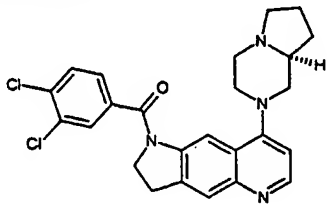


A solution of (S)-(-)-6-amino-4-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinoline (D2, 70 mg, 0.26 mmole) in DCM was treated with dichlorobenzoyl chloride (113 mg, 0.54 mmole) and DMAP (1 mg, 8 mmole). After 15 h the solution was diluted with DCM and washed with saturated aqueous $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$), filtered and concentrated to dryness *in vacuo*. Silica gel chromatography (DCM/MeOH 93:7) gave the title compound as a white glass, which was taken up into acetone, treated with dry ethereal HCl and concentrated to dryness, giving the hydrochloride salt as a white powder (60 mg, 52%).

^{1}H NMR (free base) (400 MHz, $CDCl_3$) δ (ppm): 9.45 (s, 1H), 8.68 (s, 1H), 8.58 (d, 1H), 8.00 (s, 1H), 7.91 (d, 1H), 7.72-7.66 (m, 2H), 7.41 (d, 1H), 6.83 (d, 1H), 3.68 (br. d, 1H), 3.61 (br. d, 1H), 3.12-3.00 (m, 3H), 2.72 (t, 1H), 2.56 (td, 1H), 2.38-2.30 (m, 1H), 2.20-2.14 (m, 1H), 1.90-1.80 (m, 2H), 1.75-1.65 (m, 1H), 1.51-1.40 (m, 1H). MS: m/z (MH) = 441.

Example 2

(S)-(-)-1-[(3,4-Dichlorophenyl)carbonyl]-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E2)

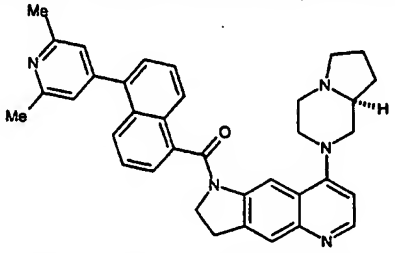


A solution of (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 100 mg, 0.34 mmole) in DCM (4 ml) was treated with pyridine (0.5 ml), 3,4-dichlorobenzoyl chloride (161 mg, 0.77 mmole) and DMAP (1.5 mg, 12 mmole) and heated at reflux under argon. After 17 h the solution was cooled and washed with 5% citric acid solution. The organic phase was dried ($MgSO_4$), filtered and concentrated to dryness *in vacuo*. Silica gel chromatography (DCM/MeOH 19:1) gave the title compound (44 mg, 28%).

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.85-8.75 (br. s, 1H), 8.63 (d, 1H), 7.87 (s, 1H), 7.76 (s, 1H), 7.56 (d, 1H), 7.45 (dd, 1H), 6.83 (d, 1H), 4.17 (br. s, 2H), 3.64 (br. s, 2H), 3.40-3.27 (m, 2H), 3.18-3.02 (m, 4H), 2.71 (br. s, 2H), 2.32 (br. d, 1H), 1.93-1.79 (m, 3H), 1.49 (br. s, 1H). MS: m/z (MH) = 467.

Example 3

(S)-(-)-2,3-Dihydro-1-[5-(2,6-dimethylpyridin-4-yl)naphth-1-ylcarbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E3)

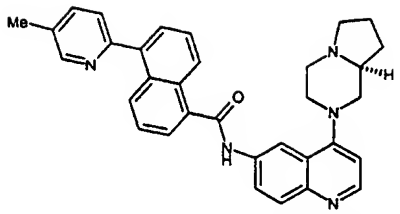


The title compound was prepared from (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 100 mg, 0.34 mmole) and 5-(2,6-dimethylpyridin-4-yl)naphthoyl chloride (D14, 150 mg, 0.51 mmole) using a similar procedure to Example 2, as a cream coloured solid (31 mg, 16%).

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.09 (s, 1H), 8.64 (d, 1H), 8.00 (d, 1H), 7.94 (d, 1H), 7.86 (s, 1H), 7.64-7.54 (m, 3H), 7.45 (d, 1H), 7.11 (s, 2H), 6.88 (d, 1H), 3.97-3.69 (br. m, 3H), 3.46-3.22 (br. m, 3H), 3.19-3.10 (br. m, 2H), 2.81-2.76 (br. m, 2H), 2.64 (s, 6H), 2.62-2.46 (br. m, 2H), 2.33-2.28 (m, 1H), 2.00-1.87 (br. m, 2H), 1.84-1.76 (br. m, 1H), 1.58-1.50 (br. m, 1H). MS: m/z (MH) = 554.

Example 4

(S)-(-)-6-[5-(5-Methylpyridin-2-yl)naphth-1-oylamino]-4-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinoline (E4)

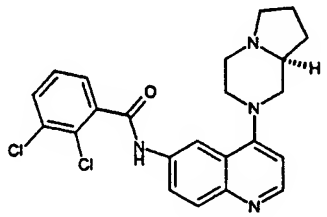


A solution of (S)-(-)-6-amino-4-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinoline (D2, 85 μmole), 5-(5-methylpyridin-2-yl)naphthoic acid (D16, 255 μmole) and 1-hydroxybenzotriazole (255 μmole) in DCM (3 ml) was treated with 1,3-diisopropylcarbodiimide (255 μmole) and shaken for 48 h at room temperature. The solution was passed through a solid phase cation exchange (SCX) cartridge, which was washed with MeOH. Elution with 2M NH_3 in MeOH, followed by evaporation *in vacuo* gave the title compound as a pale brown glass (46%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.81 (s, 1H), 8.66 (d, 1H), 8.57 (s, 1H), 8.47 (d, 1H), 8.42 (d, 1H), 8.03 (d, 1H), 7.90 (d, 1H), 7.78 (d, 1H), 7.70-7.58 (m, 3H), 7.45 (d, 2H), 7.31 (d, H), 6.89 (d, 1H), 3.78 (br. d, 1H), 3.69 (br. d, 1H), 3.22-3.05 (br. m, 3 H), 2.81-2.65 (m, 1H), 2.67 (s, 1H), 2.51-2.43 (br. m, 1H), 2.26 (q, 1H), 1.99-1.70 (br. m, 3H), 1.50 (m, 1H). MS: m/z (MH) = 514.

Example 5

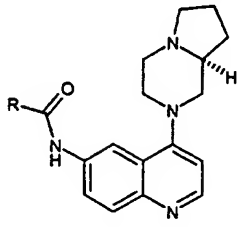
(S)-(-)-6-(2,3-Dichlorobenzoylamino]-4-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinoline (E5)

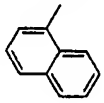
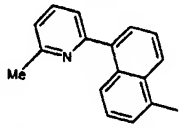
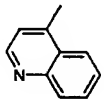
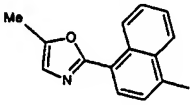


The title compound was prepared from (S)-(-)-6-amino-4-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinoline (D2, 85 μmole) and 2,3-dichlorobenzoic acid (255 μmole) using a similar procedure to Example 4, as a yellow glass (67%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.74 (d, 1H), 8.72 (d, 1H), 8.58 (d, 1H), 7.97 (d, 1H), 7.61 (dd, 1H), 7.53-7.48 (m, 2H), 7.23 (t, 1H), 6.84 (d, 1H), 3.74 (br. d, 1H), 3.66 (br. d, 1H), 3.19-3.02 (m, 3 H), 2.72 (t, 1H), 2.62 (td, 1H), 2.44-2.33 (br. m, 1H), 2.22 (q, 1H), 1.95-1.74 (br. m, 3H), 1.48 (m, 1H). MS: m/z (MH) = 441, 442, 443, 444.

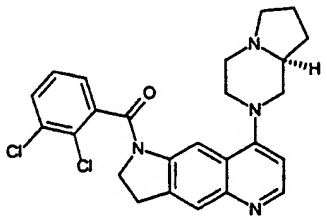
Examples E6 – E9 were prepared using a similar procedure to that described for Example 4.



Example	R	MS	Example	R	MS
E6		423	E8		514
E7		424	E9		504

Example 10

(S)-(-)-1-(2,3-Dichlorobenzoyl)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E10)



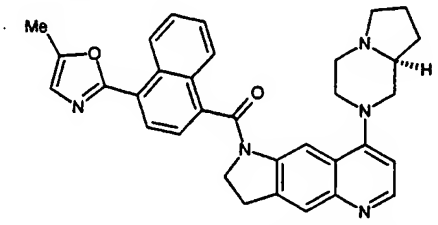
The title compound was prepared from (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 85 µmole), and 2,3-dichlorobenzoic acid (255 µmole) using a similar procedure to Example 4, as a yellow glass (51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.93 (s, 1H), 8.62 (d, 1H), 7.86 (s, 1H), 7.57 (dd, 1H), 7.37 (m, 2H), 6.85 (d, 1H), 4.05-3.65 (br. m, 3H), 3.34 (t, 2H), 3.24-3.11 (br. m, 2H), 2.74 (br. t, 2H), 2.52 (br. s, 1H), 2.30 (q, 1H), 1.98-1.74 (m, 5H), 1.60-1.48 (br. m, 1H).

MS: m/z (MH) = 467, 468, 469, 470.

Example 11

(S)-(-)-2,3-Dihydro-1-[4-(5-methyloxazol-2-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E11)

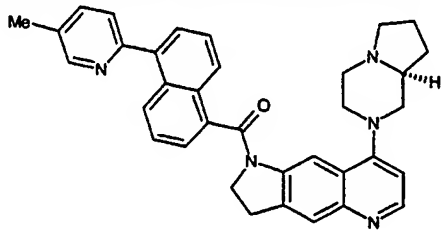


The title compound was prepared from (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 85 μmole) and 4-(5-methyloxazol-2-yl)-1-naphthoic acid (D21, 255 μmole) using a similar procedure to Example 4, as a brown glass (47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.39 (d, 1H), 9.09 (s, 1H), 8.64 (d, 1H), 8.24 (d, 1H), 7.99 (d, 1H), 7.84 (s, 1H), 7.71-7.56 (m, 3H), 7.05 (s, 1H), 6.88 (d, 1H), 3.90-3.67 (br. m, 3H), 3.26 (t, 2H), 3.19-3.09 (br. m, 2H), 2.80 (br. t, 2H), 2.49 (s, 3H), 2.31 (br. m, 1H), 2.00-1.87 (br. m, 3H), 1.60-1.48 (br. m, 1H). MS: m/z (MH) = 530.

Example 12

(S)-(-)-2,3-Dihydro-1-[5-(5-methylpyridin-2-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline trifluoroacetate (E12)

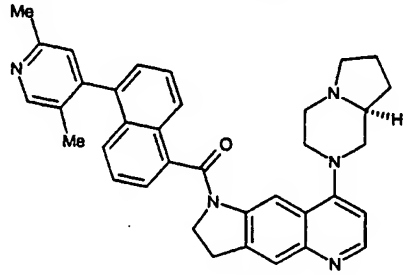


The title compound was prepared from (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 85 μmole), and 5-(5-methylpyridin-2-yl)-1-naphthoic acid (D16, 255 μmole) using a similar procedure to Example 4. The compound was further purified using reverse phase HPLC and isolated as the trifluoroacetate salt, as a pale brown glass (20%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 9.01 (s, 1H), 8.83 (s, 1H), 8.71 (s, 1H), 8.25 (s, 1H), 8.23 (dd, 1H), 8.02 (d, 1H), 7.88 (br. d, 1H), 7.64-7.54 (m, 4H), 7.58 (d, 1H), 7.25 (d, H), 4.23 (br. d, 1H), 4.10-3.65 (br. m, 10 H), 3.43 (t, 2H), 2.90 (s, 3H), 2.51-2.43 (br. m, 1H), 2.35-2.18 (br. m, 3H). MS: m/z (MH) = 540.

Example 13

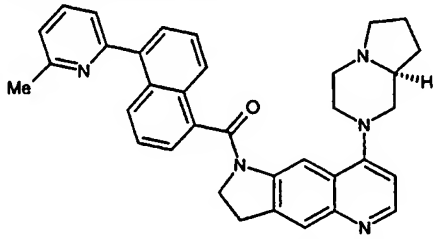
(S)-(-)-2,3-Dihydro-1-[5-(2,5-dimethylpyridin-4-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E13)



The title compound was prepared from (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 85 μmole), and 5-(2,5-dimethylpyridin-4-yl)-1-naphthoic acid (D22, 255 μmole) using a similar procedure to Example 4, as a pale brown glass (35%). MS: m/z (MH) = 554.

Example 14

(S)-(-)-2,3-Dihydro-1-[5-(6-methylpyridin-2-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E14)

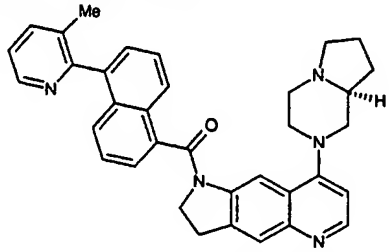


The title compound was prepared from (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 85 μmole), and 5-(6-methylpyridin-2-yl)-1-naphthoic acid (D17, 255 μmole) using a similar procedure to Example 4, as a yellow glass (46%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 9.07 (s, 1H), 8.63 (d, 1H), 8.16 (d, 1H), 7.98 (d, 1H), 7.90 (s, 1H), 7.75 (t, 1H), 7.66-7.49 (m, 4H), 7.37 (d, 1H), 7.25 (d, 1H), 6.90 (d, 1H), 3.87-3.76 (br. m, 3H), 3.37-3.19 (br. m, 4H), 3.00-2.87 (br. m, 2H), 2.69 (s, 3H), 2.42 (q, 1H), 2.08-1.83 (br. m, 3H), 1.71-1.60 (br. m, 1H). MS: m/z (MH) = 540.

Example 15

(S)-(-)-2,3-Dihydro-1-[5-(3-methylpyridin-2-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E15)

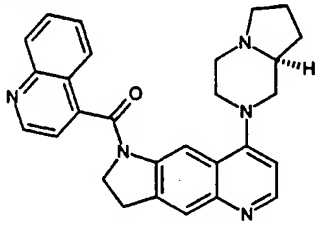


The title compound was prepared from (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 85 μmole), and 5-(3-methylpyridin-2-yl)-1-naphthoic acid (D23, 255 μmole) using a similar procedure to Example 4, as a pale yellow glass (64%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 9.09 (s, 1H), 8.65-8.60 (m, 2H), 8.03 (d, 1H), 7.86 (s, 1H), 7.74-7.59 (m, 4H), 7.51 (s, 1H), 7.49 (d, 1H), 7.32 (dd, 1H), 6.88 (d, 1H), 3.90-3.71 (br. m, 3H), 3.32-3.13 (br. m, 5H), 2.87-2.73 (br. m, 2H), 2.64-2.52 (m, 1H), 2.38-2.26 (m, 2H), 2.08-1.83 (br. m, 3H), 2.07 (s, 3H), 1.71-1.60 (br. m, 1H). MS: m/z (MH) = 540.

Example 16

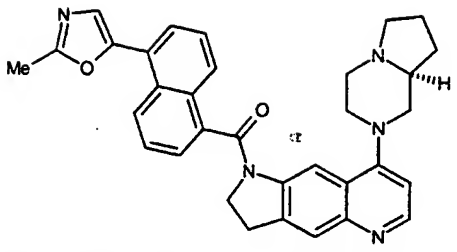
(S)-(-)-2,3-Dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)-1-(quinolin-4-ylcarbonyl)pyrrolo[2,3-*g*]quinoline (E16)



The title compound was prepared from (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 85 μmole), and 4-quinoline carboxylic acid (255 μmole) using a similar procedure to Example 4, as a yellow glass (72%).
MS: m/z (MH) = 450.

Example 17

(S)-(-)-2,3-Dihydro-1-[5-(2-methyloxazol-5-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E17)

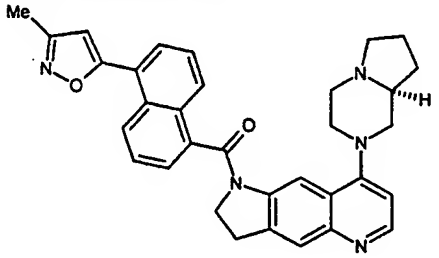


The title compound was prepared from (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 85 μmole), and 5-(2-methyloxazol-5-yl)-1-naphthoic acid (D34, 255 μmole) using a similar procedure to Example 4, as a yellow glass (36%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 9.08 (s, 1H), 8.62 (d, 1H), 8.39 (m, 1H), 7.97 (d, 1H), 7.84 (s, 1H), 7.78 (d, 1H), 7.66-7.55 (m, 3H), 7.31 (s, 1H), 6.88 (d, 1H), 3.85-3.67 (br. m, 3H), 3.25 (t, 2H), 3.21-3.11 (br. m, 2H), 2.79 (br. t, 2H), 2.62 (s, 3H), 2.30 (m, 1H), 1.98-1.75 (br. m, 3H), 1.60-1.45 (br. m, 1H). MS: m/z (MH) = 530.

Example 18

(S)-(-)-2,3-Dihydro-1-[5-(3-methylisoxazol-5-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E18)

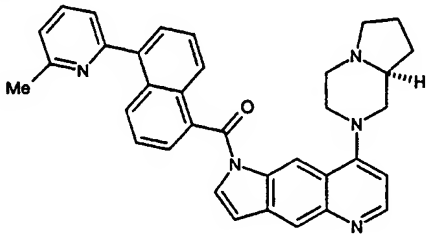


The title compound was prepared from (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 85 μmole), and 5-(3-methylisoxazol-5-yl)-1-naphthoic acid (D36, 255 μmole) using a similar procedure to Example 4, as a yellow glass (26%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 9.06 (s, 1H), 8.63 (d, 1H), 8.41 (m, 1H), 8.07 (d, 1H), 7.90 (s, 1H), 7.84 (d, 1H), 7.67-7.58 (m, 3H), 6.89 (d, 1H), 6.49 (s, 1H), 3.90-3.69 (br. m, 3H), 3.35-3.15 (br. m, 4H), 2.79 (br. m, 2H), 2.46 (s, 3H), 2.40-2.30 (m, 1H), 2.02-1.80 (br. m, 3H), 1.71-1.55 (br. m, 1H). MS: m/z (MH) = 530.

Example 19

(S)-(-)-1-[5-(6-methylpyridin-2-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E19)

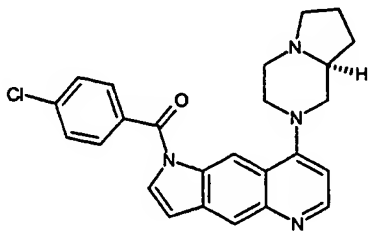


A stirred solution of (S)-(-)-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D37, 150 mg, 510 μmole) in dry DMF (15 ml) at 4 under Ar was treated with NaH (18 mg, 0.77 mmole) and warmed to room temperature for 30 mins. A solution of 5-(6-methylpyridin-2-yl)-1-naphthoyl chloride (D38, 190 mg, 0.77 mmole) in DMF (5 ml) was added and stirring continued for 20 h. The solution was partitioned between EtOAc and sat. aq. $NaHCO_3$ solution. The organic phase was washed with sat. aq. $NaHCO_3$ solution, water, and brine, dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The product was obtained after silica gel chromatography eluting with DCM followed by DCM/MeOH 9:1, as a yellow gum (15 mg, 5%).

^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 9.37 (s, 1H), 8.82 (d, 1H), 8.50 (d, 1H), 8.31 (d, 1H), 7.94 (d, 1H), 7.78-7.57 (m, 4H), 7.40 (d, 1H), 7.27 (d, 1H), 7.17 (d, 1H), 6.97 (d, 1H), 6.73 (d, 1H), 3.95-3.80 (m, 2H), 3.49-3.24 (m, 5H), 3.07 (m, 2H), 2.71 (s, 3H), 2.14-1.94 (m, 4H).
MS: m/z (MH) = 430.

Example 20

(S)-(-)-1-(4-chlorobenzoyl)-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E20)



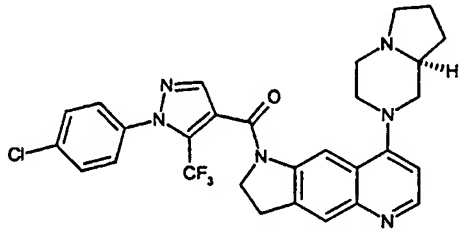
A stirred solution of (S)-(-)-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D37, 150 mg, 510 μmole) in dry DMF (15 ml) was treated with DMAP and 4-chlorobenzoyl chloride (0.38 mmole). After 18 h the solution was partitioned between DCM and saturated aqueous $NaHCO_3$ solution. The organic phase was washed with brine, dried over MgSO4,

filtered and concentrated to dryness *in vacuo*. The product was obtained after silica gel chromatography eluting with DCM followed by DCM/MeOH 19:1, as a yellow gum (19 mg, 21%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 9.10 (s, 1H), 8.76 (d, 1H), 8.28 (d, 1H), 7.74 (d, 2H), 7.56 (d, 2H), 7.49 (dd, 1H), 6.90 (d, 1H), 6.82 (d, 1H), 3.73 (m, 2H), 3.16 (m, 2H), 2.78 (m, 2H), 2.36 (m, 2H), 1.90 (m, 4H), 1.54 (m, 1H). MS: m/z (MH) = 430.

Example 21

(S)-(-)-2,3-Dihydro-1-[2-(4-chlorophenyl)-3-trifluoromethylpyrazole-4-carbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E21)

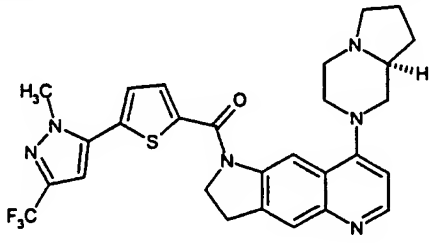


The title compound was prepared from (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 170 μmole), and 2-(4-chlorophenyl)-3-trifluoromethylpyrazole-4-carboxylic acid (250 μmole) using a similar procedure to Example 4, as a yellow glass (52%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.90 (s, 1H), 8.63 (d, 1H), 7.90 (s, 1H), 7.86 (s, 1H), 7.51 (d, 2H), 7.44 (d, 2H), 6.85 (d, 1H), 4.18-4.06 (br. t, 2H), 3.78-3.63 (br. m, 2H), 3.37 (t, 2H), 3.20-3.05 (br. m, 3H), 2.70-2.78 (br. t, 2H), 2.50-2.60 (br. m, 1H), 1.79-1.97 (br. m, 4H), 1.45-1.57 (br. m, 1H). MS: m/z (MH) = 568.

Example 22

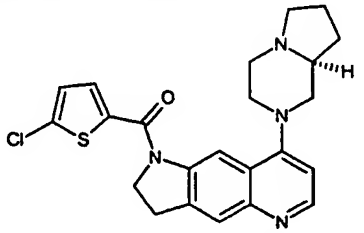
(S)-(-)-2,3-Dihydro-1-[5-(2-methyl-5-trifluoromethylpyrazol-3-yl)-thiophen-2-carbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E22)



The title compound was prepared from (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 170 μmole), and 5-(2-methyl-5-trifluoromethylpyrazol-3-yl)-thiophen-2-carboxylic acid (250 μmole) using a similar procedure to Example 4, as a yellow glass (80%).
^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.64 (s, 1H), 8.60 (d, 1H), 7.83 (s, 1H), 7.58 (d, 1H), 7.31 (d, 1H), 6.85 (s, 1H), 6.82 (d, 1H), 4.48 (t, 2H), 4.02 (s, 3H), 3.69-3.57 (br. m, 2H), 3.39 (t, 2H), 3.20-3.02 (m, 3H), 2.75-2.63 (m, 2H), 2.50-2.40 (br. m, 1H), 2.25-2.21 (br. m, 1H), 1.92-1.76 (br. m, 3H), 1.44-1.55 (m, 1H). MS: m/z (MH) = 553.

Example 23

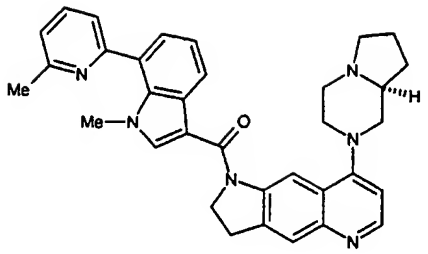
(S)-(-)-2,3-Dihydro-1-(5-chlorothiophen-2-carbonyl)-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E23)



The title compound was prepared from (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 170 μmole), and 5-chlorothiophen-2-carboxylic acid (250 μmole) using a similar procedure to Example 4, as a yellow glass (66%).
^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.62 (s, 1H), 8.60 (d, 1H), 7.83 (s, 1H), 7.40 (d, 1H), 6.95 (d, 1H), 6.81 (d, 1H), 4.42 (t, 2H), 3.68-3.56 (br. m, 2H), 3.39 (t, 2H), 3.20-3.00 (m, 3H), 2.76-2.64 (m, 2H), 2.47-2.39 (br. m, 1H), 1.98-1.79 (br. m, 4H), 1.46-1.59 (m, 1H).
MS: m/z (MH) = 438.

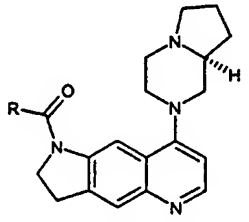
Example 24

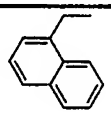
(S)-(-)-2,3-Dihydro-1-[1-methyl-7-(2-methylpyridin-6-yl)indol-3-carbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E24)

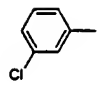
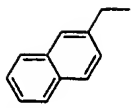
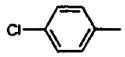
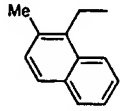
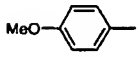
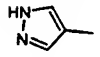
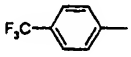
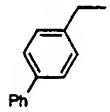
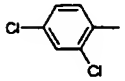
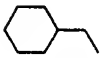
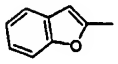
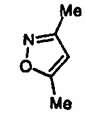
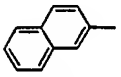
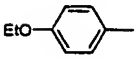
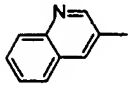
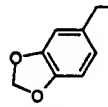
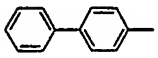
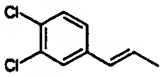
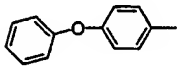
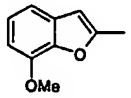
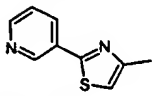
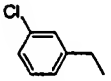
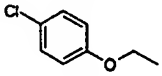
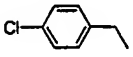
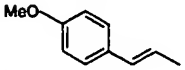
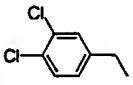
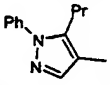


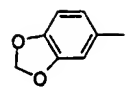
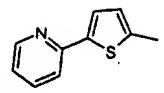
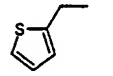
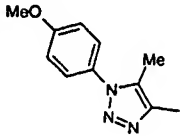
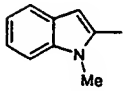
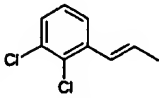
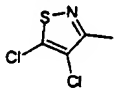
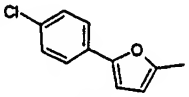
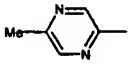
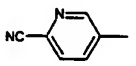
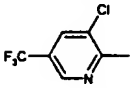
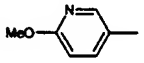
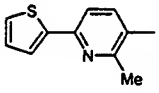
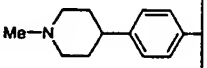
A stirred solution of (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 45 mg, 0.15 mmole) in anhydrous toluene (5 ml), under argon, was treated with a solution of methyl 1-methyl-7-(6-methylpyridin-2-yl)indole-3-carboxylate (D42, 54 mg, 0.19 mmole) in anhydrous toluene (5 ml). $AlMe_3$ (0.15 ml, 0.29 mmole) was added *via* a syringe and the mixture was heated at reflux, under argon for 18 h. The reaction was cooled and poured directly onto a silica sep pak (5 g), which was eluted with 5% MeOH/DCM. Fractions containing the product were combined, concentrated to dryness *in vacuo* and the residue further purified by preparative tlc, eluting with 15% MeOH/DCM, giving the title compound as a yellow solid (20 mg, 24%).
^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.58 (d, 1H), 8.39 (br. s, 1H), 7.98-7.93 (m, 2H), 7.70 (dd, 1H), 7.51 (s, 1H), 7.37 (d, 1H), 7.26-7.19 (m, 3H), 6.83 (d, 1H), 4.37 (br. t, 2H), 3.71 (br. d, 1H), 3.46 (s, 3H), 3.35 (br. t, 2H), 3.38-3.23 (br. m, 4H), 2.97 (br. s, 2H), 2.70-2.40 (br. s, 2H), 2.65 (s, 3H), 2.07-1.70 (br. m, 4H).MS: m/z (MH) = 543.

Examples E25 - E72 were prepared in parallel using a similar procedure to that described for Example 4.



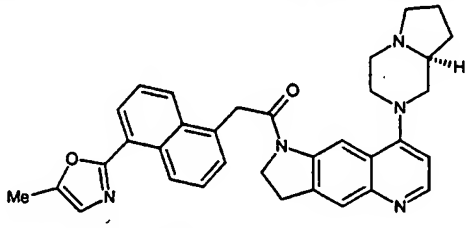
Example	R	MS	Example	R	MS
E25		432	E26		463

E27		432	E28		463
E29		432	E30		477
E31		429	E32		389
E33		467	E34		489
E35		467			
E36		389	E37		419
E38		439	E39		418
E40		449	E41		443
E42		450	E43		457
E44		475	E45		493
E46		491	E47		469
E48		447	E49		483
E50		447	E51		463
E52		447	E53		455
E54		482	E55		507

E56		443	E57		482
E58		419	E59		510
E60		452	E61		493
E62		414	E63		474
E64		414			
E65		414	E66		499
E67		415	E68		424
E69		502	E70		430
E71		496	E72		496

Example 73

(S)-(-)-2,3-Dihydro-1-[5-(5-methyloxazol-2-yl)naphth-1-ylacetyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E73)



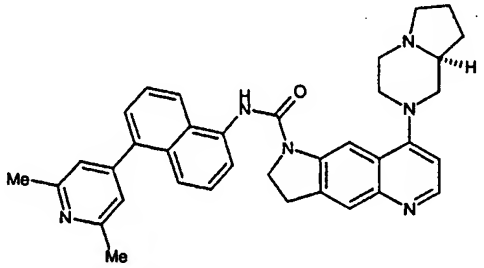
The title compound was prepared from (S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 85 µmole), and 5-(5-methyloxazol-2-

yl)naphth-1-ylacetic acid (D27, 255 μmole) using a similar procedure to Example 4, as a pale brown glass (70%).

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 9.24 (d, 1H), 8.87 (s, 1H), 8.60 (d, 1H), 8.18 (d, 1H), 8.14 (d, 1H), 7.80 (s, 1H), 7.64-7.48 (m, 3H), 6.99 (s, 1H), 6.82 (d, 1H), 4.37 (s, 2H), 4.17 (t, 3H), 3.68 (br. t, 2H), 3.34 (t, 2H), 3.20-2.99 (m, 3H), 2.71 (t, 2H), 2.47 (s, 3H), 2.31 (q, 1H), 1.95-1.70 (br. m, 3H), 1.55-1.42 (br. m, 1H). MS: m/z (MH) = 544.

Example 74

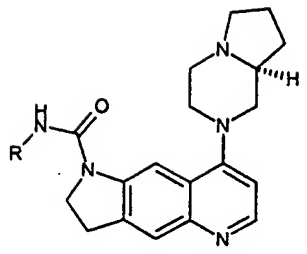
(S)-(-)-2,3-Dihydro-1-[5-(2,6-dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (E74)

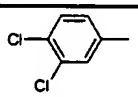
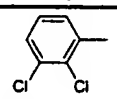
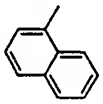
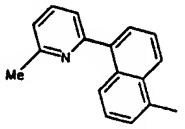
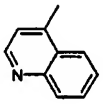
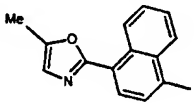


(S)-(-)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline (D10, 100 mg, 340 μmole) in DCM (10 ml) was added to a solution of 5-(2,6-dimethylpyridin-4-yl)naphth-1-yl isocyanate (D15, 0.38 mmole) in DCM (10 ml). The mixture was heated at reflux under argon for 16 h, then concentrated *in vacuo* to afford the crude product. This was purified by silica gel chromatography, eluting with DCM:MeOH (93:7), to give the title compound as a cream coloured solid (80 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.56 (d, 1H), 8.47 (s, 1H), 8.03 (d, 1H), 7.85 (d, 1H), 7.83 (s, 1H), 7.70 (d, 1H), 7.55 (dd, 1H), 7.47 (dd, 1H), 7.40 (d, 1H), 7.09 (s, 1H), 7.08 (s, 2H), 6.82 (d, 1H), 4.30 (t, 2H), 3.64 (d, 1H), 3.56 (d, 1H), 3.44 (t, 2H), 3.07-2.98 (m, 3H), 2.69 (t, 1H), 2.62 (s, 6H), 2.55 (dt, 1H), 2.32 (br. m, 1H), 2.14 (q, 1H), 1.87-1.61 (br. m, 3H), 1.42-1.38 (m, 1H). MS: m/z (M-H) = 567.

Examples E75 - E80 were prepared in parallel using a similar procedure to that as described for Example E74.



Example	R	MS	Example	R	MS
E75		482	E76		482
E77		463	E78		554
E79		464	E80		544

(*R*)-Enantiomers of Examples 23, 29, 33 and 35 were prepared by coupling (R)-(+)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline, prepared from (R)-(+)-octahydropyrrolo[1,2-*a*]pyrazine (*J. Med. Chem.*, 1993, **36**, 2311) according to the procedures described in D7 - D10, with carboxylic acids using procedures similar to that described in Example 4.

Pharmacological Data

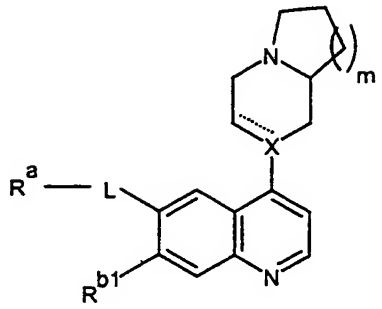
The affinities of the compound of this invention was determined using the radiolabelled binding assay as described above.

5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} Receptor Binding

All Examples had pKi values > 7.5 at 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors.

CLAIMS

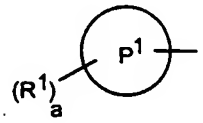
1. A compound of formula (I) or a salt thereof:



(I)

in which R^a is selected from a group of formula (i) or (ii);

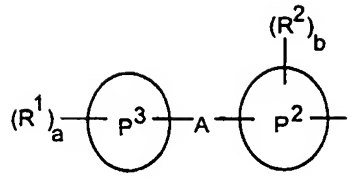
Group of formula (i)



(i)

wherein P^1 is phenyl, bicyclic aryl, C_{3-6}cycloalkyl, a 5 to 7 membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur;
R^1 is halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, hydroxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, NO_2, CF_3, CN, SR^9, SOR^9, SO_2R^9, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $CONR^{10}R^{11}$, $CONR^{10}(CH_2)_cCO_2R^{11}$, $(CH_2)_cNR^{10}R^{11}$, $(CH_2)_cCONR^{10}R^{11}$, $(CH_2)_cNR^{10}COR^{11}$, $(CH_2)_cCO_2C_{1-6}$alkyl, $CO_2(CH_2)_cOR^{10}$, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CONR^{10}R^{11}$, $CR^{10}{=}NOR^{11}$, $CNR^{10}{=}NOR^{11}$, where R^9, R^{10} and R^{11} are independently hydrogen or C_{1-6}alkyl and c is 1 to 4; and
a is 0, 1, 2 or 3;

Group of formula (ii)



(ii)

wherein P^2 and P^3 are independently phenyl, bicyclic aryl, a 5 to 7 membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic heterocyclic group containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;
A is a bond, O, $S(O)_n$ where n is 0 to 2, carbonyl, CH_2 or NR^4 where R^4 is hydrogen or C_{1-6}alkyl;
R^1 and R^2 are independently as defined above for R^1 in formula (i); and
a and b are independently 0, 1, 2 or 3;

L is a group of formula
- Y-C(= O)-DG - or -C(= O)-DG- or -DG-C(= O)-
in which Y is NH, NR^5 where R^5 is C_{1-6}alkyl, or Y is CH_2, O, CH = CH, or OCH_2;
D is nitrogen, carbon or a CH group, G is hydrogen or C_{1-6}alkyl providing that D is nitrogen or a CH group, or G together with R^{b1} forms a group W where W is $(CR^{16}R^{17})_t$ in which t is 2, 3 or 4 and R^{16} and R^{17} are independently hydrogen or C_{1-6}alkyl or W is $(CR^{16}R^{17})_u$-J where u is 0, 1, 2 or 3 and J is oxygen, sulphur, $CR^{16}=CR^{17}$, $CR^{16}=N$, $=CR^{16}O$, $=CR^{16}S$ or $=CR^{16}$-NR^{17} provided that u is not 0 when J is oxygen or sulphur;

R^{b1} is hydrogen or together with G forms a group W as defined above;
X is nitrogen, carbon or a CH,

—— is a single bond when X is nitrogen or CH and is a double bond when X is carbon.
m is 1, 2 or 3.

2. A compound according to claim 1 in which X is a nitrogen atom and m is 1.

3. A compound according to any of the preceding claims in which within the definition of L the group D is nitrogen and the group G is hydrogen or together with R^{b1} forms a further group $(CH_2)_2$.

4. A compound according to any of the preceding claims in which R^a is a group of formula (i) and P^1 is a phenyl, naphthyl, quinolyl, pyridyl or thienyl group.

5. A compound according to any one of claims 1 – 3 in which R^a is a group of formula (ii) and P^2 is a phenyl, naphthyl, pyridyl, thienyl or furyl group

6. A compound according to claim 1 which is:
(S)-(-)-N-[4-(Octahydropyrrolo[1,2-a]pyrazin-2-yl)quinolin-6-yl]-3,4-dichlorobenzamide,
(S)-(-)-N-[4-(Octahydropyrrolo[1,2-a]pyrazin-2-yl)quinolin-6-yl]-3,4-dichlorobenzamide,
(S)-(-)-N-[4-(Octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinolin-6-yl]-3,4-dichlorobenzamide,
(S)-(-)-2,3-Dihydro-1-[5-(2,6-dimethylpyridin-4-yl)naphth-1-ylcarbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-6-[5-(5-Methylpyridin-2-yl)naphth-1-oylamino]-4-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinoline,
(S)-(-)-6-(2,3-Dichlorobenzoylamino]-4-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)quinoline,
(S)-(-)-1-(2,3-Dichlorobenzoyl)-2,3-dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-[4-(5-methyloxazol-2-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline
(S)-(-)-2,3-Dihydro-1-[5-(5-methylpyridin-2-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline trifluoroacetate
(S)-(-)-2,3-Dihydro-1-[5-(2,5-dimethylpyridin-4-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-[5-(6-methylpyridin-2-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)-1-(quinolin-4-ylcarbonyl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-[5-(2-methyloxazol-5-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-[5-(3-methylisoxazol-5-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-1-[5-(6-methylpyridin-2-yl)naphth-1-oyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-1-(4-chlorobenzoyl)-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,

(S)-(-)-2,3-Dihydro-1-[2-(4-chlorophenyl)-3-trifluoromethylpyrazole-4-carbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-[5-(2-methyl-5-trifluoromethylpyrazol-3-yl)-thiophen-2-carbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-(5-chlorothiophen-2-carbonyl)-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-[1-methyl-7-(2-methylpyridin-6-yl)indol-3-carbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-[5-(5-methyloxazol-2-yl)naphth-1-ylacetyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline,
(S)-(-)-2,3-Dihydro-1-[5-(2,6-dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-8-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)pyrrolo[2,3-*g*]quinoline
or a pharmaceutically acceptable salt thereof.

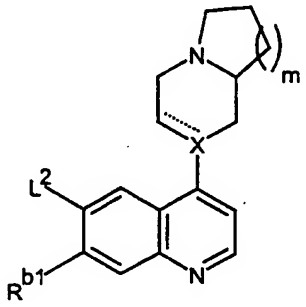
7. A process for the preparation of a compound of formula (I) which comprises:

(a) where L is -C(=O)-DG - or -DG-(C=O)-, coupling a compound of formula (II):

R^a -L^1

(II)

with a compound of formula (III):



(III)

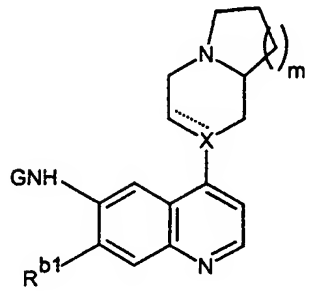
in which R^a, R^{b1}, X and m are as defined in formula (I) and L^1 and L^2 contain the appropriate functional groups which are capable of reacting together to form the L moiety; or

(b) where L is - Y -C(=O)-DG in which D is nitrogen and Y is NH, coupling a compound of formula (IV):

R^a -NC(=O)

(IV)

in which R^a is as defined in formula (I) or a protected derivative thereof, with a compound of formula (V):



(V)

in which R^{b1}, X, m and G are as defined in formula (I), or a protected derivative thereof; or

(c) where L is - Y -C(=O)-DG - in which D is nitrogen and Y is NH or NR^5, reacting a compound of formula (VI)

$$R^a\text{-}NH_2 \text{ or } R^a\text{-}NR^5H$$

(VI)

in which R^a and R^5 are as defined in formula (I) with a compound of formula (V) together with an appropriate urea forming agent; or

(d) where L is - Y -C(=O)-DG - in which D is nitrogen and Y is CH_2 or O, reacting a compound of formula (VII):

$$R^a\text{-}Y\text{-}(C{=}O)\text{-}L^3$$

(VII)

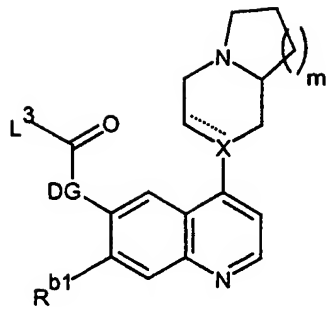
in which R^a is as defined in formula (I), and L^3 is an appropriate leaving group, with a compound of formula (V); or

(e) where L is - Y -C(=O)-DG - in which D is CH and Y is NH, reacting a compound of formula (VI):

$$R^a\text{-}NH_2$$

(VI)

in which R^a is as defined in formula (I) with a compound of formula (VIII):



(VIII)

in which D, G, R^{b1}, X and m are as defined in formula (I) and L^3 is an appropriate leaving group;

and optionally thereafter:

- removing any protecting groups;
- forming a pharmaceutically acceptable salt.

8. A compound according to any of claims 1 to 6 for use in therapy.

9. A compound according to any of claims 1 to 6 for use in the treatment of depression.

10. A pharmaceutical composition which comprises a compound according to any of claims 1 to 6 and a pharmaceutically acceptable carrier.